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AMINO ACIDURIA, CONGENITAL DEFECTS, AND MENTAL RETARDATION

A PRELIMINARY REPORT

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FOR the past three years a clinic for brain-damaged children has been held in conjunction with our cerebral palsy services at Children's Hospital.* Admitted to the clinic for study and evaluation have been several children whose development and behavior have aroused our curiosity. They are children who have a number of anomalies, each of which is not handicapping, but the multiplicity of anomalies and the associated mental retardation have been inexplicable. A combination of symptoms and findings has suggested that these children might fall into a borderline group of one of three other fairly well-known entities, namely, (1) Lowe's syndrome,[1] (2) phenylketonuria, (3) Fanconi's syndrome.[2] It was decided therefore to screen these children for output of amino acid nitrogen. This was made possible through the cooperation of Dr. Harold Harper at the University of California.

A total of fourteen children have been screened. Out of these, seven have been found to have an abnormal output of amino acid nitrogen. One of these is not included in this report because of inadequate follow-up to date. One milligram amino nitrogen per pound is considered a normal output. In some cases only twelve-hour specimens were obtained. In order to reduce all to a single standard, the estimated output of amino acid nitrogen was doubled for these cases. This may give a slightly false value, but in the determinations made on twelve-hour specimens, the output even for that period was above the normal for twenty-four hours. The following case reports are illustrative of the patients and the findings.

CASE REPORTS

CASE 1.—K. S., female, born Sept. 14, 1954. The patient was 16 months of age at the time of the report. K. S. was the first-born female infant, the father and mother of whom are living and well. The mother had a Scandinavian heritage, the father an Italian one. There was no history of familial disease, neurological or mental abnormalities. The baby was born six weeks prematurely, weighing 5 pounds

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5 ounces. At birth it was noted that she had a number of minor anomalies, one of which was a small tumor in the right nostril, another a dimple in the midline of the upper lip, the deficiency of the tissue to the right of this resembling an incomplete harelip. She had been treated for allergies prior to coming to us for examination. Her development was reported to be somewhat delayed.

On physical examination this child weighed 27 pounds. Her height was 31 inches, head circumference 45.8 centimeters. She has blond, reddish hair, a flattening of the right posterior skull causing an asymmetry of the head. There were two pedunculated skin tags 2 to 3 mm. in size, anterior to the left ear. The eyes had a peculiar appearance, slanting downward laterally in a manner opposite to that of a Mongol. The tissues about the eyes appeared taut and the eye slits narrowed. There was excessive tearing. The anterior part of the nose was flattened, with a slight separation in the septum as if improperly fused. There was a dimple in the midline of the upper lip and an absence of deep tissue of the right upper lip, giving the appearance of a harelip which has skin covering it though the tissues underneath are incompletely fused. There was a small tumor mass in the right nostril arising from the midline. She had erupted twelve teeth. There was no pathology demonstrable in the lungs, heart, abdomen, or genitals. The feet and legs were normal. The reflexes were normal. She was making attempts to pull herself up but had not yet started cruising. She made sounds but had no words. She was responsive to a degree and was described as a good baby. She was obviously not functioning at the level of the average 16-month-old infant. A blood examination revealed 10.8 grams, 69 per cent, white blood cells 9,500 polymorphonuclears 36, lymphocytes 63, eosinophil 1. Urine analysis showed clear urine, albumin negative, sugar negative, pH 8.0. Phenylpyruvic acid test was negative. Amino acid nitrogen output for twenty-four hours was 106 mg., the normal rate being 1 mg. per pound. This child weighing 27 pounds had an output between three and four times that of the normal.

CASE 2.—M. E., male, born Sept. 6, 1949. The age of the patient at the time of the report was 6 years. This child was the result of a first pregnancy. The mother was living and well and had a long American heritage. The father was a native of Iran. The maternal grandmother was congenitally deaf. This was a term baby, weight 6 pounds 8 ounces. At birth no positive abnormal physical findings were noted except that the child had a peculiar look resembling a little, old man. He had a good deal of hirsutism. He was a poor eater, cried a great deal, and at each visit a comment was made on his odd appearance. This was variously described as having an "Andy Gump" jaw, the look of a little, old man, etc. At 3 months of age he began to gain weight. At that time he was noted to have a rather persistent strabismus, a very high, narrow palate, and rather widely spaced eyes. As time passed it was noted that his achievement was below normal. He did not walk until he was 2 years of age, he was over 3 years before he said any words and he was 5 before he was even partially toilet trained. At 6 years of age he weighed 68 pounds. On physical examination he looked obese, he still had a marked hirsutism, his eyes were myopic, teared a great deal, and were widely spaced, suggesting hypertelorism. He had a very high, narrow palate. No abnormalities had been noted of the heart or lungs. The genitals were small in proportion to his large torso. The extremities, likewise, looked small for his body. The bone age was reported to be 4 years as compared with his chronological age of 6. X-ray of the skull showed a tendency to ocular hypertelorism. A routine blood count

showed no abnormality. Urine analysis on Jan. 6, 1956, yielded 142 mg. of amino acid nitrogen for twelve hours, which, if calculated for the twenty-four-hour period, would be 284. This yield for a child weighing 68 pounds is four times that of the normal. Chemical studies of the blood and urine follow: serum creatinine, 0.78 mg. per 100 c.c. (normal 1 to 2 mg. per 100 c.c.); serum phosphorus, 3.65 mg. per 100 c.c. (normal up to 5 mg. per cent); serum alkaline phosphatase, 5.04 units Bodansky (normal 5 to 12). Urine: 1,050 c.c. in twelve hours—qualitative sugar, negative; urine creatine, 36 mg. per 100 c.c. or 0.37 Gm. per twelve hours; urine creatinine, 35 mg. per 100 c.c. or 0.37 Gm. per twelve hours; urine phosphorus, 35.3 mg. per 100 c.c. or 0.37 Gm. per twelve hours.

CASE 3.—E. W., female, born May 17, 1954. The patient's age at the time of this report was 20 months. This was a child who was placed for adoption and the family history was unknown. The pregnancy was at term, birth weight 9 pounds 7 ounces. A persistent strabismus was noted at birth, but without other abnormalities she was considered acceptable for adoption. She was brought in by the prospective parents when 11 months of age because by comparison with another child in the family her development appeared slow. Her weight at that time was 24 pounds, height 32½ inches, head circumference 46½ centimeters. She had a marked strabismus which was being treated by patching one eye. She obviously paid very little attention to her environment, including the mother. Aside from her behavior she was a pretty little girl with blond curly hair, a marked strabismus, but no other abnormalities of the eyes, confirmed by the opthalmologist. The fontanel was almost closed. There were eight teeth present, no abnormalities of the heart and lungs were found, spleen and liver were not palpable, feet and legs were normal, reflexes normal. Bone age was reported as follows: "While the hand alone suggests 11 to 12 months of age, the presence of 2-year-old centers indicate a more advanced maturation." X-ray of the skull was reported as normal. Electroencephalogram revealed a mildly abnormal tracing for the age of 11 months with some evidence that the underlying dysfunction involved the right more than the left hemisphere. The blood count revealed a hemoglobin of 12.4 or 86 per cent, red cells 4,520,000, white cells 9,000, with polymorphonuclears 13, eosinophils 3, lymphocytes 82, monocytes 2. Urine analysis yielded an acid reaction, sugar negative, albumin slightest possible trace, red blood cells 0 to 1, and white blood cells 4 to 8. Test for phenylpyruvic acid was negative. Spinal fluid examination showed: 1 white cell, sugar 72.8 mg. per 100 c.c., protein 18.1 mg. per 100 c.c., chloride 710 mg. per 100 c.c. The amino acid nitrogen output was 48 mg. in twelve hours or 96 mg. in twenty-four hours for a child weighing 28 pounds. At present her behavior tends to autism. She shows greater interest in objects than people. She has formed no definite attachment to her foster mother, and has not objected to placement in a new environment. She is not yet walking, although making definite progress toward it. She babbles but has no real speech. Psychometric studies place her in a borderline mental defective classification.

CASE 4.—N. S., female, born June 1, 1951. The patient's age at the time of examination was 4½ years. The mother and father were living and well. There was no familial history of neurological diseases or anomalies. N. S. was the result of a third pregnancy. There was a male sibling 10 years of age, living and well. A miscarriage was recorded between the first pregnancy and the present patient. A younger sibling who was 4 months of age was reported as normal. The pregnancy was full term,

delivery normal, birth weight 7 pounds 5 ounces. No abnormalities were noted at birth but fairly early it was recognized that this child's achievement was not following the same pattern as her brother's. She did not walk until 21 months. Her speech was markedly delayed.

On examination her weight was 42 pounds. She had a marked strabismus, although ophthalmologic examination otherwise was reported as negative. She walked with a somewhat stooped gait, her head carried forward. There was hyperflexibility of her joints. No abnormalities were noted of the heart and lungs. There was no splenomegaly or hepatomegaly. Reflexes were normal. A psychometric determination places her motor age at 30 to 36 months; adaptive 21 to 24 months; language 21 minus months; social behavior 24 to 30 months. The electroencephalogram showed a mildly abnormal to borderline tracing pointing to some nonfocal dysfunction within the cerebral hemispheres. X-ray of the skull was reported as normal. Bone age corresponded to the chronological age. The bony structure was delicate but no other abnormalities noted. Blood count revealed a hemoglobin of 12 grams or 80 per cent, red blood cells 3,980,000, white blood cells 9,000, polymorphonuclears 66, eosinophils 4, lymphocytes 28, monocytes 2. Urine analysis revealed a cloudy urine, alkaline reaction, specific gravity 1.026, albumin negative, sugar green with amorphous precipitate, acetone negative, occasional red blood cells, and rare white blood cells. The phenylpyruvic acid test was negative. The amino acid nitrogen output was 69 mg. in twenty-four hours for a child who weighed 42 pounds. This was not nearly as high as the others and might be considered as a borderline normal. Unfortunately the child was from out of town and the slight sugar reduction in the urine could not be traced further.

CASE 5.—J. B., male, born Nov. 29, 1949. The patient at the time of examination was 6 years of age. Family history revealed that the mother was living and well. The father was living and well except that he had a history of having his right eye enucleated for some abnormality present since birth. Recently a history was obtained that the mother's sister lost a baby at birth and the anatomical diagnosis on this infant was multiple congenital anomalies as follows: omphalocele, bilateral hydronephrosis and hydroureters, agenesis of the bladder, of the appendix, of ascending and transverse colon, and malrotation of the third phase of the intestinal rotation. Mrs. B. and her sister were Rh negative. J. B. was an only child. The prenatal and birth histories were normal. The child at birth had clubfeet and a tumor of the right eye which resulted in enucleation of the eye at an early age. He also had had repair of the feet before he was seen at our clinic. His feeding was reported as difficult in infancy and pyloric stenosis had been considered. However, after the first feeding difficulty was over he gained well. He sat up at 15 months but did not walk until he was almost 4 years. He still used only a few words and there was marked difficulty for anyone except those constantly with him to understand him. He was only partially toilet trained.

On physical examination he was a large, very well-developed child, whose right eye had been enucleated. The left eye was normal. The head was normally shaped. The dentition was normal for his age. There were no abnormalities of the heart and lungs or of the abdomen. The feet showed good operative result. Present height was 48 inches, weight 60 pounds. An electroencephalogram showed a disorganized pattern with many low to medium voltage borderline to abnormal slow 4 to 6 per second cycles. Psychological evaluation on the Cattell Infant Scale showed a development of 16 to 18 months and the Vine-

land Social Maturity Scale 12 to 18 months. The blood count was 10.7 grams or 74 per cent, red blood cells 3,930,000, white blood cells 10,600, polymorphonuclears 54, eosinophils 5, lymphocytes 40, monocyte 1. Urine analysis revealed reaction acid, albumin slightest possible trace, sugar negative. Amino acid nitrogen determination yielded 160 mg. in twenty-four hours for a child weighing 60 pounds. Chemical studies of the blood and urine were as follows: serum creatinine, 0.92 mg. per 100 c.c. (normal 1 to 2 mg. per 100 c.c.); serum phosphorus, 3.86 mg. per 100 c.c.; serum alkaline phosphatase, 4.53 units Bodansky.

Urine: 685 c.c., twenty-four-hour output—qualitative sugar negative; urine creatine, 23 mg. per 100 c.c., 0.16 Gm. per twenty-four hours; urine creatinine, 97 mg. per 100 c.c., 0.66 Gm. per twenty-four hours; urine phosphorus, 85 mg. per 100 c.c., 0.58 Gm. per twenty-four hours.

Case 6.—P. R., female, born June 1, 1951. The patient's age at the time of the report was 4½ years. Family history revealed mother and father were living and well. There was no history of familial disease. Mother was Rh negative. P. R. was a full-term, normally delivered baby. Birth weight was 6 pounds 5 ounces. She was a slow eater and gained poorly. She cried a great deal. Her first tooth was cut at 7 months. At 12 months she weighed 18½ pounds. She then was, and has remained, prone to infection. She started walking at 13 months, was noted to be slow in her general interest. At the age of 19 months it was noted that she had an enlargement of her left breast which on palpation had the feel and on inspection the appearance of an early adolescent enlargement. A few months later the right breast also enlarged and then they both gradually subsided. Shortly thereafter she had a bladder infection and investigation of the kidney tract revealed a congenital hypoplasia of the right kidney with congenital right urethral stricture. There was also noted an absence of the anterior portion of the vaginal ring. Her facial appearance was somewhat peculiar. She had a persistent epicanthal fold with wide spacing of the eyes and a flattening of the tip of the nose, with an indentation, as if improperly fused. Her development was slow for the age of 4½ years. She still speaks very poorly and continues to act infantile. A psychometric determination placed her at approximately 3½ years. The bone age was very slightly retarded. No bone abnormalities of the skull were noted. Urine analysis showed: albumin 1 plus, pH at one time 5, at another 6, sugar negative. Amino acid nitrogen determination yielded 65 mg. in twenty-four hours for a child weighing 34 pounds which is approximately twice that of normal.

The other patient, P. C., weighing 28 pounds, had an amino acid nitrogen output of 69 mg. in twenty-four hours.

A total of fourteen children have been studied for amino acid nitrogen output. The other seven with normal output were chosen for various reasons. One had blindness, mental retardation, and muscle atonia. The history, however, was that development was normal until an encephalitis occurred at the age of 5 months. Three in the negative group had congenital anomalies of the central nervous system, two had histories of anoxia preceding and at birth. In one of the cases the mental retardation is still unexplained.

DISCUSSION

Amino aciduria may occur without mental retardation as, for instance, in Fanconi's syndrome[2] and in cases reported by Luder and Sheldon.[3] Mental retardation occurred in Lowe's cases and is a part of the picture of phenylketonuria. In our clinic with approximately 150 children registered in the past three years, fourteen chil-

dren were selected to be screened and seven of these have been found to have an increased output of amino acid nitrogen. The histories in two of the positive cases suggest the possibility of genetic origin. In Case 5 there appeared congenital anomalies on both sides of the family. In Case 2 a grandmother had congenital deafness which may or may not be significant. Although the physical findings in these children vary considerably, some of the children resemble each other as much as Mongols do. All of the children have some abnormality of the eyes or the surrounding tissues of the eye, such as hypertelorism, abnormal slant, etc. The rest of the anomalies vary from multiple, rather marked anomalies to only strabismus. In the group are children who are stunted in their physical development as well as children who are overweight. All of the children show mental retardation, although the degree of this varies greatly. The most striking thing about their mental development is that they appear much more retarded at a later age than early. Blood chemistry in two cases shows no definite abnormality in creatine, creatinine, phosphorus, and alkaline phosphatase. Chemical analysis of the urine likewise shows an output of creatine, creatinine, and phosphorus that is within the normal range. The pH of the urine has been reported both as acid and alkaline, with pH's varying from 5 to 8. The sugar when done has been qualitatively negative except in two instances when it showed slight reduction on routine test. The finding of a relatively large number of retarded children with an abnormal output of amino acid nitrogen opens up a large field for investigation. It is obvious that the amino acids of both the blood and urine must be studied in great detail in a large series of cases in order to determine whether or not there is a correlation between either the kind or the amount of amino acid output and the symptoms. The kidney function must likewise be investigated and a variety of metabolic studies should be conducted. The genetics of this condition needs elucidation. Even though no immediate therapy suggests itself, it at least opens up an area for investigation that promises to bear some results in a field that has been exceedingly discouraging.

SUMMARY

A series of six cases with varying degrees of congenital anomalies, mental retardation, and abnormal output of amino acid nitrogen in the urine have been described. Further investigation of these children and their families is contemplated. Studies of metabolism and kidney function as well as detailed investigation of the amino acids in the blood and urine will be made. The families will be studied for hereditary traits.

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COMPLICATIONS OF SMALLPOX VACCINATION AND THEIR TREATMENT WITH VACCINIA IMMUNE GAMMA GLOBULIN

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SMALLPOX is still prevalent throughout the world. At least 400,000 cases are estimated to occur annually, chiefly in Asia, Africa, and Central and South America. The mortality mostly ranges from 30 to 60 per cent. Steadily improving intercontinental traffic, with shortened traveling time for passengers, increases the risk of transmitting the disease from one country to another. For example, Indonesia was practically free from smallpox in 1942, owing to compulsory vaccination. At that time, the events of war and later political circumstances caused a stop in the vaccination program. In 1948, many infants and children were not vaccinated and older persons partially lacked immunity. In this year an epidemic broke out on Sumatra and was transmitted to Java, where a severe epidemic with many deaths occurred.[1] Consequently, the advantages of compulsory smallpox vaccination seem to greatly outweigh the drawbacks of the complications sometimes associated with it. These are, as a rule, not dangerous and cause no residual damage, but they may occasionally have a more severe course. In Sweden, smallpox vaccination is compulsory, and over 100,000 primary vaccinations are performed each year (Table I).

The complications that may occur are described in the following.

INOCULATION VACCINIA

This complication arises through contact from the primary lesions to the skin or mucous membranes of the vaccinated subject or persons in his surroundings. The manifestations and possible damage that may occur are essentially dependent on the site of the secondary lesions. Involvement of the eyelids is not uncommon (Fig. 1). The often marked edema of the eyelids and face may then be alarming, but it usually subsides rapidly without specific therapy, as do most of the relevant lesions. Localization to the cornea is more serious, since it may result in permanently impaired vision. In the series accounted for in Table I, there was only one instance of this complication during a five-year period.

Secondary lesions in the oral cavity, tongue (Fig. 2), vulva and perianal region (Fig. 3) are painful and may present diagnostic problems, but they are seldom associated with any therapeutic difficulties.

A common feature of generalized vaccinia, eczema vaccinatum, and gangrenous vaccinia is the tendency to hematogenic spreading. This also seems to apply to fetal vaccinia. It

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would therefore seem justified to group all these complications under the heading of generalized vaccinia.[2] Since, however, both the clinical features and the prognosis differ essentially in all these conditions, it is important to make a sharp distinction between them.

Fig. 1.—Vaccinia of the eyelid in a child aged 1 year 9 months.

Fig. 2.—Oral lesions. This 5-year-old child had infected herself after touching the vaccination lesion of a playmate. Incubation period: 6 days. Further course uncomplicated without specific therapy.

GENERALIZED VACCINIA

Generalized vaccinia in the true meaning of the term is characterized by ordinary development of the primary reaction. A rash on otherwise normal skin generally appears six to fourteen days after vaccination. Fully developed, the clinical picture resembles that of actual smallpox, since the secondary lesions are all at the same stage of development. Healing is, however, rapid; it is usually completed at the same time as that of the primary lesion and leaves no scars.

In fatal cases, death occurs within two to three weeks of the onset.[2] The mortality is stated to be low.[3] Greenberg[4] investigated the incidence of complications in a New York series from 1947, when about 5 million vaccinations were performed during a short period. Of forty-five cases denoted as generalized vaccinia, thirty-eight had eczematous lesions, and should therefore have been classified as eczema vaccinatum. Such lesions were lacking in seven cases, which therefore belong to the group of generalized vac-

Fig. 3.—Perianal lesions. This 1-year-old girl had infected herself. Admitted to hospital on account of febrile convulsions. Negative findings at lumbar puncture. Discharged healthy.

cinia in the true sense. No deaths occurred in the latter group.

ECZEMA VACCINATUM

In this condition, the vaccinia virus is usually transmitted to an area of eczema from the primary lesion or through contact with a newly vaccinated person. Healthy areas may also become involved by hematogenic spreading. The respiratory tract has been stated to be a possible port of entry.[5] The patients are often severely ill,[6] and disfiguring scars may result. The mortality rate in infants is given as 40 per cent,[3] in other series as 25 to 30 per cent.[6] Bergman and Lindahl[6] in Sweden reported a series of twelve cases of eczema vaccinatum; one patient died and three were badly scarred. In Greenberg's[4] series of thirty-eight cases, two infants died; they were 4 and 6 months old, respectively. They had not been vaccinated, but had been infected by contact with newly vaccinated persons.

GANGRENOUS VACCINIA

Gangrenous vaccinia (progressive vaccinia, vaccinia necrosum) progresses slowly for weeks or months, with necrosis of the skin and underlying tissues at and around the site of vaccination. Metastatic processes appear in the skin, mucosa, and internal organs, and osteomyelitis has also been observed.[2] This complication is exceedingly rare. A prerequisite for its occurrence seems to be a severe disturbance in the patient's immunologic response, with a greatly reduced ability to form specific antibodies. Barbero and associates[2] have ascribed the first description of this condition to Acland and Fisher[7] (1893) in their report entitled "A Case of Generalized Vaccinia." The former authors were able to find altogether eight cases in the literature, all with a fatal outcome. They described one case of their own; the patient recovered after treatment with vaccinia immune gamma globulin.

A survey of the literature would presumably disclose additional cases. In Greenberg's[4] publication, I found a report of a 66-year-old man who died one month after vaccination, presenting a similar clinical picture; death was stated to be caused by sepsis and bronchopneumonia. Kozinn and co-workers[8] reported another case with a fatal outcome. The collected statistics to date would therefore comprise eleven cases, ten of them with a fatal outcome. Electrophoresis in four cases showed agammaglobulinemia in three patients.[8]

Without specific therapy, the prognosis is poor, and not even ordinary gamma globulin preparations or transfusions from vaccinated donors have led to positive results.[8]

FETAL VACCINIA

Fetal vaccinia is a rare complication. Only two cases have been encountered in the literature, one described by Lynch[9] (1932) and the other by MacDonald and MacArthur[10] (1953). In both cases the mother had been vaccinated during pregnancy. The infants were premature and had widespread skin lesions; judging by the descriptions, they exhibited similarities to the clinical picture in gangrenous vaccinia. The infants were in extremely poor condition at birth and died shortly afterward.

In connection with a smallpox epidemic in west Scotland in 1950, MacArthur[11] investigated the influence of vaccination on the results of pregnancy in 203 women who, judging by

the scars, had reacted with pustule formation. His results were extremely interesting. Of the 136 women who had been vaccinated in the fourth or subsequent months of pregnancy, only seven gave birth to abnormal infants (four premature infants, one stillbirth, one death soon after birth and one with brain damage during labor). This did not differ significantly from the expected incidence in a normal series. Only one of the thirty-three women who had been vaccinated during the first four weeks of pregnancy, or who became pregnant within two weeks of vaccination, had a miscarriage; the other thirty-two gave birth to normal infants. On the other hand, it was found that, in the group of thirty-four women vaccinated between the fourth and twelfth weeks of pregnancy, no less than seventeen (50 per cent) had a course deviating from the normal (ten abortions, five stillbirths, one with congenital malformations, and one premature). The remaining seventeen had full-term children, healthy at birth. Thus, in this series, there was considerable risk for the fetus if the mother, without earlier acquired immunity, was vaccinated during the first trimester of pregnancy. In women vaccinated early in pregnancy, but without signs of a positive reaction, the results of pregnancy were normal.[12]

POSTVACCINATION ENCEPHALITIS

Postvaccination encephalitis is an unusual complication. In Sweden, about two cases occur each year (Tables I and II).

It may be inferred from Table II that the incidence decreased from 3.3 to 1.9 per 100,000 vaccinations in a comparison between the periods 1924 through 1946 and 1947 through 1954. Since the mortality rate in both periods was about 14 per cent, this implies an approximate decrease in the number of deaths by about 50 per cent. Thus, during the former period, there were 0.46 deaths per 100,000 vaccinations, and in the latter only 0.23.

The usual clinical evaluation of the cases, which is based on the time relation between vaccination and signs of cerebral inflammatory lesions cannot in itself provide any information about the causative mechanism. As a rule, it is not possible to culture the virus from the brain in fatal cases, nor from the cerebrospinal fluid showing inflammatory changes. According to Smadel,[13] this type of encephalitis is

TABLE I. NUMBER OF PRIMARY VACCINATIONS AND INCIDENCE OF COMPLICATIONS IN SWEDEN IN 1950 THROUGH 1954

YEAR	NO. OF PRIMARY VACCINATIONS	NO. OF CASES OF POSTVACCINATION ENCEPHALITIS*	NO. OF OTHER COMPLICATIONS†	NO. OF COMPLICATIONS PER 100,000 VACCINATIONS
1950	115,419	- (-)	84 (-)	73 (-)
1951	107,415	1 (-)	70 (-)	65 (-)
1952	108,136	2 (1)	70 (1)	67 (1.8)
1953	100,247	2 (-)	53 (-)	55 (-)
1954	113,133	4 (1)	53 (1)	49 (1.8)
Total	544,350	9 (2)	330 (2)	60 (0.9)

*Cases reported to Royal Medical Board and verified by State Bacteriological Laboratory. All such cases are notifiable.

†Cases known to Royal Medical Board through annual reports from hospitals and cottage hospitals for contagious diseases, eye departments of hospitals, children's hospitals, and pediatric departments. Figures in parentheses denote deaths.

identical to that found in other virus diseases and in rabies therapy. Consequently, it does not seem possible to ascribe it to a direct action of the virus.

VACCINATION EXANTHEMA

These exanthemas not infrequently resemble the rash of measles or scarlatina, and may cause the patient to be admitted to a hospital for infectious diseases before the correct diagnosis is made. No treatment is necessary, and the exanthema subsides at the same time as the vaccination reaction.

CASE 1.—A girl, aged 5 years 5 months, with epilepsy. High fever developed in connection with vaccination, and she died in status epilepticus. No grounds existed for suspecting post-vaccination encephalitis.

CASE 2.—A boy, aged 7 years 9 months, with imbecility and extrapyramidal syndrome. He was vaccinated on October 13. On October 22, there was a rise in temperature to 41.3° C., with loss of consciousness and convulsions. Death occurred within a few hours. The local course of vaccination showed nothing noteworthy. Autopsy disclosed inflammation of the tonsils and bronchi sufficient to account for death.

TABLE II. POSTVACCINATION ENCEPHALITIS IN SWEDEN IN 1924 THROUGH 1954

Period	1924-1946*	1947-1954	1924-1954
No. of primary vaccinations	2,155,293	856,493	3,011,786
Age group (yr.)	No. of cases of encephalitis per age group Deaths in parentheses		
0-1	6 (-)	2 (1)	8 (1)
1-2	7 (1)	- (-)	7 (1)
2-3	9 (-)	1 (-)	10 (-)
3-4	5 (-)	- (-)	5 (-)
4-5	4 (-)	1 (-)	5 (-)
5-6	10 (3)	4 (1)	14 (4)
6-7	11 (3)	3 (-)	14 (3)
7-8	12 (3)	2 (-)	14 (3)
8-9	2 (-)	2 (-)	4 (-)
≧9	4 (-)	- (-)	4 (-)
No statement of age	1 (-)	1 (-)	2 (-)
Total	71 (10)	16 (2)	87 (12)
No. of cases of encephalitis per 100,000 vaccinations	3.3	1.9	2.9
No. of deaths per 100,000 vaccinations	0.46	0.23	0.4
Mortality in per cent of cases of encephalitis	14.1	13.3	14.0

*Collected by Heinertz,[17] partly from earlier publications by Lichtenstein and Huss[14] and Olin.[15, 16]

VACCINATION COMBINED WITH OTHER ILLNESSES

If other infections occur in connection with vaccination, there is usually no cause for alarm, although the patient should be kept under strict supervision. Any existing brain damage may be unfavorably affected. Life-threatening conditions may develop. A brief account of three cases with a fatal outcome is given in the following.

CASE 3.—A man, aged 20 years. He received primary vaccination and fell ill with appendicitis at about the same time. Operation was performed, but after successive exacerbation the patient died. Autopsy showed an intra-abdominal abscess and septic pulmonary emboli.

In none of the cases did autopsy disclose any influence of vaccination

on the fatal outcome. The possibility that it was a contributory factor cannot, however, be ruled out.

Another type of course is illustrated by the following case.

CASE 4.—A girl, aged 6 years 6 months, received primary vaccination on May 10. On May 19, she had fever and felt ill. On May 23, a rash appeared, as well as gastrointestinal disturbances in the form of vomiting and loose defecations. She was admitted to hospital on May 25. There was then a normal local reaction, with a scab at the site of vaccination. Numerous ecchymoses were present on the trunk, extremities, soles of the feet, and palms. There was macroscopic hematuria. The patient was hospitalized for six months under the diagnosis of vaccinia, Schoenlein-Henoch purpura, acute nephritis, and nosocomial rhinopharyngitis. She was discharged in good condition.

Purpura has been observed in a number of virus infections, even those of a mild type. A hemorrhagic diathesis is characteristic of the extremely dangerous form of smallpox known as hemorrhagic smallpox. In the case reported here, an individual tendency to a hemorrhagic diathesis may have existed. This would have produced the clinical picture described, but the possibility of, for example, a concurrent infection of some other origin must also be taken into account.

INCIDENCE OF COMPLICATIONS IN SWEDEN

The following procedure was used to estimate the incidence of complications of vaccination occurring in Sweden, of such a nature that hospitalization was considered necessary. A collocation was made from the annual reports of all the hospitals and cottage hospitals for contagious diseases throughout the country, of the eye departments of hospitals, and of children's hospitals and pediatric departments (Table I). Since the nomenclature was not uniform in these reports, all the complications reported, with the exception of postvaccination encephalitis, have been assembled under one heading: other complications. The cases of encephalitis consist of those reported to the Royal Medical Board and verified by the State Bacteriological Laboratory.

There were two deaths in the group of other complications. Both were children who had not been vaccinated, but who had been infected by the virus through contact with newly vaccinated persons.

CASE 5.—A boy, aged 9 months. He had suffered from eczema on his face since 2 months of age. On April 20, he came into contact with his mother's newly vaccinated younger siblings. On April 22, variola-like lesions appeared on his face, and subsequently spread to his arms and legs. On admission to hospital on April 26, there were closely spaced lesions on the face and forearms, and several efflorescences on the tongue and soft palate. Aureomycin therapy was instituted. There was some improvement during the first few days, although he had hyperpyrexia. On April 30, a sudden exacerbation occurred, and the patient died.

CASE 6.—A girl, aged 1 year. She had had eczema on her cheeks since about 2 months of age. One week before admission to hospital (two to three weeks after her sister had been vaccinated) a rash resembling that of chicken pox appeared, as well as fever. On the three days prior to admission, her temperature was up to 40.6° C. On admission on November 18, her general condition was affected, and she had large, encrusted infiltrations on her face, neck, and thighs. Vesicles the size of a peppercorn were present on the abdomen, hands, and arms. Penicillin was given, as well as local

application of sulfonamides, and subsequently Aureomycin. The lesions improved, but the temperature swung between 38 and 41° C. After becoming increasingly lethargic for twenty-four hours, the child died on November 25.

To show the nature of the complications of vaccination causing admission to the largest hospital for contagious diseases in Sweden, the admissions to Epidemisjukhuset, Stockholm, during the five-year period 1950 through 1954 are recorded in Table III. No deaths occurred. The great majority of cases had a mild and uncomplicated course. In the "Vaccination + Other Illness" group, the diagnoses were as follows: scarlatina

Fig. 4.—Eczema vaccinatum in a 16-year-old girl. She also had acute myocarditis. Treated with antibiotics.

Fig. 5.—Same case as shown in Fig. 4. After treatment.

TABLE III. SURVEY OF FIFTY-FOUR CASES OF COMPLICATED VACCINATION, TREATED AT EPIDEMISJUKHUSET, STOCKHOLM IN 1950 THROUGH 1954 (NO DEATHS)

YEAR	STRONG REACTION	VACCINATION + EXANTHEMA	VACCINATION + OTHER ILLNESS	VACCINATION + PURPURA + NEPHRITIS	SECONDARY LESIONS		GENERALIZED VACCINIA	ECZEMA VACCINATUM*	POSTVACCINATION ENCEPHALITIS
					IN VACCINATED PERSONS	IN OTHER PERSONS			
1950	2	2	3	1	–	–	–	–	–
1951	4	–	3	–	2	–	1	1	1
1952	1	1	3	–	7	2	–	5	1
1953	1	–	–	–	1	–	–	1	1
1954	2	–	2	–	5	–	–	1	–
Total	10	3	11	1	15	2	1	8	3

*Concurrent acute myocarditis in two cases.

in two cases, impetigo in two cases, one case each of measles, chicken pox, pneumonia, pharyngitis, erythema nodosum, and scarlatina observation, and one "carrier" (β-hemolytic streptococci). Two of the eight patients with eczema vaccinatum had transient clinical and electrocardiographic signs of acute myocarditis.[18]

PREVENTIVE MEASURES AGAINST COMPLICATIONS

In order to prevent complications of smallpox vaccination, instructions given must be carefully followed. By making the inoculation at a site inaccessible to the patient, e.g., on the back below the spina scapulae, he can be prevented from transferring infectious material with his hands from the lesion to other parts of the body.

Persons with eczema should not be vaccinated, nor should those who cannot be isolated from other persons with eczema. Cerebral disturbances, such as epilepsy, are contraindications to vaccination. Primary vaccination should be done during the first year of life, when the risk of encephalitis is minimal. Persons who, owing to frequent severe infections, can be suspected to have a decreased ability to form antibodies or possibly agammaglobulinemia should be investigated in this respect before vaccination is performed.[19] Owing to the risk of fetal damage and possible abortion, women should not be vaccinated in early pregnancy; this question may arise in connection with travel to countries requiring vaccination for an entry permit.[20]

Even if every precaution is taken, complications cannot always be avoided. Particularly if patients with smallpox were to enter the country, widespread mass vaccination might become necessary. A not inconsiderable number of earlier unvaccinated persons would then have to be vaccinated, thereby increasing the risk of eczema vaccinatum, for example. The majority of cases of this type reported by Greenberg[4] were unvaccinated eczema patients who had been in contact with newly vaccinated persons.

Thus, situations may not infrequently arise in which it is desirable to have access to a specific therapeutic method, aimed at counteracting the possible injurious effect of vaccination.

Already Bergman and Lindahl[6] (1941) gave blood from newly vaccinated persons in severe cases of eczema vaccinatum, with a view to affecting the course by means of passive immunization. This principle was applied in three cases, with recovery in two. In the third case, a 7-month-old boy, a hemorrhagic diathesis appeared despite improvement of the skin lesions, and the patient died. This method has subsequently been used at Epidemisjukhuset, Stockholm, in severe cases of eczema vaccinatum, and no deaths from this complication have been recorded since then.[21]

Kempe[22] (1954) reported the properties of his vaccinia immune gamma globulin prepared by fractionation of blood from newly vaccinated persons. In vitro experiments showed it to have a high content of antibodies to the variola and vaccinia viruses, about ten to twenty times higher than that of ordinary gamma globulin preparations.[23] Together with Barbero and associates,[2] he successfully treated a 4½-year-old boy with gangrenous vaccinia, an otherwise invariably fatal complication. Antibodies to the vaccinia virus were entirely lacking in this patient. After administration of

altogether five 10 ml. doses of this specific gamma globulin in the course of six weeks, the patient recovered.

Kempe[22] also used vaccinia immune gamma globulin during a smallpox epidemic in southern India. All family contacts of known cases were vaccinated. The series consisted of 133 persons; fifty-seven of them received gamma globulin after vaccination, the other seventy-six serving as controls. In the former group, two cases of smallpox occurred (3.5 per cent), in the latter, nine cases (11.8 per cent). It is true that about 80 per cent of the persons had been vaccinated earlier, so that no general conclusions can be drawn. The results nevertheless indicate that use of this preparation should be among the measures taken in certain situations to prevent smallpox when an epidemic threatens. Experience with the use of gamma globulin in other diseases has, in fact, shown that this passive prophylaxis has an immediate effect, whereas active protection requires a certain time to develop. Kempe[22] stated that the administration of gamma globulin did not affect the immunizing effect of the normal course of vaccination. Consequently, vaccination and administration of specific gamma globulin can be used concurrently in smallpox prophylaxis. This seems to be of special value when, for example, persons with a tendency to eczema must be vaccinated, owing to exposure to infection.

The case reported by Barbero and associates[2] is of great importance. The view prevailing earlier has been that administration of antibodies to cases of manifest virus disease are unable to favorably affect its course.[24] There now seem to be possibilities of producing a good effect in conditions due to a virus, when the antibody formation is defective. A comparison can be made with the experience reported by Odessky and co-workers.[25] They have reported good results of treatment with gamma globulin in, for example, cerebral complications of measles. A control series was, however, lacking. Even if their results seem to be encouraging, it is desirable for controlled investigations to be made, in order to elucidate this important question, which is of essential importance for the treatment of postvaccination encephalitis.

The value of a specific therapeutic for preventing unfavorable outcome of a prophylactic measure cannot be underestimated. This applies in particular to a compulsory measure, aimed at protecting not only the individual, but also the community as a whole.

PREPARATION OF VACCINIA IMMUNE GAMMA GLOBULIN IN SWEDEN

At my suggestion, vaccinia immune gamma globulin was prepared by the State Bacteriological Laboratory[26] as follows. (It is known as immune globulin against vaccinia.)

Blood was taken from recruits successfully vaccinated against smallpox in the spring of 1955, the multiple pressure method being used in most cases. A positive reaction was indicated by the appearance of a pustule. The blood was withdrawn four to eight weeks after vaccination; according to the investigations of Kempe,[22] the content of antibodies to the vaccinia virus is greatest at this time. After fractionation of the serum, performed by AB Kabi, Stockholm, the immune globulin was obtained in the form of a 12 per cent solution of Cohn's fraction II, of which 95 to 98 per cent

consists of gamma globulin. Each bottle contained 5 ml., corresponding approximately to 150 ml. of whole blood.

INDICATIONS FOR IMMUNE GAMMA GLOBULIN THERAPY

The indications for the use of vaccinia immune gamma globulin may be inferred from the preceding sections of this paper; they can be summarized as follows.

Prophylactically, the preparation should be given to persons with eczema if they have been in contact with newly vaccinated cases.[3] This situation may arise in a hospital ward for skin diseases and cause a minor epidemic, such as that described by Bergman and Lindahl.[6] A few cases in the series from Epidemisjukuset (Table III) derive from such a nosocomial infection in a department for skin diseases.

Persons with allergic or eczematous skin lesions, with epilepsy, or other illnesses may be in urgent need of vaccination. In this event, immune gamma globulin can suitably be given the day after vaccination, in order to mitigate the course. This also applies to vaccination of women in early pregnancy.

Therapeutically, the preparation is indicated in cases of generalized vaccinia, eczema vaccinatum and gangrenous vaccinia. Experience is hitherto lacking of the effect of vaccinia immune gamma globulin in postvaccination encephalitis. Since, however, no other specific therapy is available, it should be tried in this condition.

In secondary inoculation vaccinia, the course is usually mild, and use of the preparation seems to be warranted only in exceptional cases, for example, when there is a risk of corneal lesions.

In certain cases, there may be indications for use of the preparation if another infectious disease appears in association with vaccination.

There is reason to believe that, under certain conditions, ordinary gamma globulin preparations may serve the same purpose as specific gamma globulin, if the latter is not available. This is illustrated by the following case of generalized vaccinia treated at Kronprinsessan Lovisas Barnsjukhus.

CASE 7.—A boy, aged 9 months. He was vaccinated on June 9. On June 17, he had fever, and eruptions appeared on the trunk and extremities. On admission to hospital on June 19, the primary vaccination pustule, about 3 cm. in diameter, was surrounded by several small satellite lesions, with marked reddening and infiltration of the adjacent areas. The left shoulder was considerably swollen. A number of eruptions on the trunk and extremities, as well as the general clinical picture, gave the impression of a progressive state.

Paper electrophoresis showed the serum gamma globulin to be 5.9 per cent. Since vaccinia immune gamma globulin was still in the process of preparation, ordinary gamma globulin (Kabi X9) was given; the dose was 1 ml. per kilogram of body weight. On the following day the patient's general condition was greatly improved, the temperature was 37.0° C., and all the lesions showed regression. On the third day, the general condition was excellent (Fig. 6). When he was discharged on June 24, the lesions were practically healed and scabs had formed. The serum gamma globulin was then 10.1 per cent; at a check-up on July 7, it was 9.8 per cent. About three weeks after returning home, the patient had chicken pox without complications.

Even if it cannot be ruled out that the course would have been benign without treatment, the almost instantaneous improvement after administration of gamma globulin indicates that it had an effect. The decrease in the serum gamma globulin fraction recorded electrophoretically, together with the occurrence of generalized lesions, argue in favor of deficient

Fig. 6.—Generalized vaccinia in a 9-month-old boy with hypogammaglobulinemia (Case 7). The lesions are healing three days after administration of gamma globulin, deriving partly from blood of military personnel.

antibody formation as the factor responsible for the clinical picture.

The gamma globulin preparation used in this case was found to derive from a pool consisting partly (21 per cent) of blood collected from military personnel. In Sweden, recruits are vaccinated after induction. Consequently, there are good reasons to presume that the preparation in question had a higher content of specific antibodies than that of gamma globulin prepared from retroplacental blood, which is the usual basic material used for this purpose in Sweden.

SUMMARY

Serious complications of smallpox vaccination are rare. A survey is given of such complications, as well as of their incidence in Sweden. During a five-year period, there were two deaths from eczema vaccinatum, both unvaccinated infants, and two deaths from postvaccination encephalitis.

The importance is stressed of making a sharp distinction between generalized vaccinia, eczema vaccinatum, and gangrenous vaccinia. The clinical picture of fetal vaccinia resembles that of gangrenous vaccinia. Some cases of unusual complications and of vaccination combined with other illnesses are described.

A brief survey of the possibilities of preventing complications is given. Specific gamma globulin, prepared on the lines given by Kempe, has recently been produced in Sweden. It is intended for prevention and treatment of complications of smallpox vaccination. It is known as immune globulin against vaccinia, and is distributed by the State Bacteriological Laboratory.

The main indications for its use are listed. They are: prevention of spreading of vaccinia to eczema patients who have been in contact with newly vaccinated persons; treatment of newly vaccinated persons suffering from another serious disease, or contracting it; in cases of generalized vac-

cinia, eczema vaccinatum, and gangrenous vaccinia. The preparation should be tried when there is a risk of corneal lesions, as well as in postvaccination encephalitis, since specific therapy for these conditions is lacking. When a smallpox epidemic threatens, the preparation can presumably be used as an adjuvant in prophylaxis.

It is suggested that if specific immune gamma globulin is not available, other gamma globulin preparations should be used. They should preferably be prepared from the blood of military personnel, who are generally vaccinated on induction. Large doses should be used. A report is given of a case of generalized vaccinia with hypogammaglobulinemia, in which gamma globulin partly deriving from such a source was successfully used.

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THE TREATMENT OF DIABETIC ACIDOSIS: COMPARISON OF TREATMENT REGIMES WITH AND WITHOUT PARENTERAL POTASSIUM

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INTRODUCTION

THE role of potassium in disease states such as diabetic acidosis, alkalosis, diarrhea, and uremia has been studied extensively during the past twenty-five years. Many authors[1-5] have directed attention to the role of potassium in severe electrolyte disturbances in infants and children and have stressed the importance of including adequate amounts of potassium in parenteral therapy to correct the intracellular depletion of this ion.

It has been the feeling of one of us (A. F. H.) that when the method of treating diabetic acidosis developed by him was strictly adhered to, excellent results were obtained. In 191 consecutive cases, acidosis was rapidly recovered from, even in the six instances where death eventually occurred from causes not apparently directly related to the diabetes. There seemed little likelihood that significant hypokaliemia developed, or, if it did, that then the hypokaliemia itself deserved less attention than it has received. To secure factual data, we decided to correlate at frequent intervals and as closely as possible changes in serum potassium with electrocardiograms and the total clinical and chemical picture of fifteen children treated for severe diabetic acidosis by our "routine" method and seven children who received additional parenteral potassium. The basic principles of our "routine" method should be borne in mind and are as follows:

To Cover First Six Hours

1. *Subcutaneous administration of insulin—2 units per kilogram of body weight.* It is felt that maximally rapid abolition of ketosis is accomplished by slightly less than 1 unit and that the additional amount is an added security and is usually needed to return the blood sugar to near-normal in the first six hours.

2. *Fairly rapid intravenous administration of ⅙ molar Na lactate—30 ml. per kilogram of body weight.* This insures immediate restoration of plasma volume and flow. The metabolism of lactate makes Na almost immediately available and the subsequent continuous release of this ion leads to prompt and safe restoration of $NaHCO_3$.

3. *Later subcutaneous administration of ⅙ molar Na lactate—30 ml. per kilogram; plus hypotonic Ringer's solution—40 ml. per kilogram of body weight.* The purpose of the additional Na lactate is to provide for the needs of those children in whom the acidosis is due more to sodium deficit (from previous polyuria, aciduria, and vomit-

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ing) than to lowered serum $BHCO_3$ because of ketone acid accumulation. This also provides for the needs of those children with initial very low pH values (acidemia or uncompensated acidosis). Our previous studies have demonstrated that, if recovery must include much rise in pH, the $BHCO_3$ will be very slow in recovering unless sufficient sodium as potential alkali is administered, because of the increasing base-binding capacities of the protein and phosphate buffers noted with diminishing acidity of the blood and body fluids.[5] The purpose of the Ringer's solution is to correct chloride deficit in the *extracellular* fluid and to supply K, Ca, and Mg as well as Na in appropriate ratios. Correction of chloride deficit simultaneously with Na ion release, resulting from the metabolism of lactate and ketone acids, is depended upon to prevent $BHCO_3$ accumulation and retention beyond the zone of mild alkalosis. The hypotonicity of the Ringer's solution is designed to provide relatively more water administration than electrolyte since relatively more of the former is lost during the development of dehydration and acidosis.

To Cover the Next Six Hours

1. *More insulin—usually ½ unit per kilogram of body weight.* The second dose of regular insulin is designed to keep the subject in continued insulin effect and to bring the blood sugar to an approximately normal level by the end of the twelfth hour of therapy, when we expect most children to be able to eat their first meal. This additional insulin is needed because most of the blood sugar values in severe acidosis lie between 400 and 600 mg. per 100 ml., and at this time the operating metabolic glucose-insulin ratio is always about 2:1. Since the glucogenic effect of the lactate is fixed at 30 ml. ⅙ molar per kilogram, which is equivalent to 0.9 gram per kilogram of glucose, the routine second dose of ½ unit per kilogram of insulin usually works out very well. If extraordinary blood sugar values are encountered initially, variation of insulin dosage is made accordingly on the premise that the operating G:I ratio will continue to be 2:1 for at least another day or two.

2. *More Na lactate (30 ml. per kilogram of body weight)* is given if the serum $BHCO_3$ is less than 10 mM per liter at the end of the first six hours.

3. *More hypotonic Ringer's solution (50 ml. per kilogram of body weight)* is given if hydration is still inadequate or if the serum chloride concentration at the end of six hours is less than 90 meq. per liter.

4. *Whole blood (20 ml. per kilogram of body weight)* is administered if the red blood cell and hemoglobin values at the end of six hours indicate the need.

5. *Concentrated serum albumin* is included in the therapy if the situation at the end of six hours suggests its indication.

At Twelve Hours

1. First meal—liquid and largely fruit juice (for CHO and possibly K needs).

2. Regular or liquid diabetic meals are offered as tolerated at usual intervals with insulin HCl before each meal and at midnight, calculated on a 2:1 G:I ratio with approximate 40-20-30-10 per cent distribution.

3. Parenterally administered (intravenous or subcutaneous) D.A.S. No.

2* (for CHO, protein, water, and mineral—including K needs) if patient is unable to take food by mouth or if tube feeding seems contraindicated.

Plan of Study

Fifteen patients (Group I) in diabetic acidosis, ranging in age from 16 months to 12 years, were studied in this series. (Patient P. L. K. was admitted on two occasions.) These patients were handled in the usual manner and, of course, no added K was used in the parenteral therapy. The following blood chemical determinations were made at frequent intervals: serum true glucose, chloride, bicarbonate, nonprotein nitrogen, potassium, and sodium.

Serum true glucose was determined by the Somogyi modification of the Shaffer-Hartmann method.[7] Van Slyke's manometric method was used for serum CO_2 content determinations from which bicarbonate values were calculated. Potassium and sodium were determined with the aid of the Weichselbaum-Varney flame photometer. Electrocardiographic tracings, using the direct recording electrocardiograph, were taken in close association with the blood samples. All standard and unipolar leads were taken although only L_2 was used for demonstration. Synchronous notes were made describing color, respiratory rate and depth, pulse rate and blood pressure, skin turgor, and the state of the sensorium.

In seven patients (Group II) potassium chloride or potassium lactate was included in the initial therapy. The clinical pictures, blood chemical changes, and electrocardiograms were followed as in Group I.

*D.A.S. No. 2, a solution made by mixing equal quantities of 10 per cent dextrose, 10 per cent Amigen, and a special salt mixture. The special salt mixture contains $MgCl_2$: $6H_2O$, 0.875 Gm. per liter; Ca lactate, 3.45 Gm. per liter; and K lactate, 0.545 Gm. per liter.

GROUP I

Case 1.—W. J. H., an 8-year-old white male, was a known diabetic of two years' duration. The patient had been regulated with a mixture of protamine zinc insulin and regular insulin coupled with a rigid diet. Two days prior to admittance to St. Louis Children's Hospital the patient developed edema of the eyelids, conjunctivitis, and irritability. The next day a morbilliform erythematous rash was noted, accompanied by anorexia and fever. On the day of admittance, vomiting, abdominal pain, and extreme lethargy were noted by the parents.

Examination revealed an extremely drowsy patient who appeared acutely ill, with rapid, pauseless respirations. There was a maculopapular erythematous rash over the entire body typical of measles. The pharynx was injected and exudate was present on the tonsils. Initial blood chemical determinations revealed a serum HCO_3 of 9.4 meq. per liter and a serum true glucose of 435 mg. per 100 ml. (Table I). The tests for ketones and sugar in the urine were positive. The initial electrocardiogram was within normal limits (Fig. 1). The patient was given 2 units per kg. of regular insulin subcutaneously, 30 ml. per kg. 1/6M Na lactate intravenously, and 30 ml. per kg. 1/6M Na lactate and 50 ml. per kg. Ringer's subcutaneously.

Six hours after the initiation of therapy the patient was alert. The serum HCO_3 was 17.4 meq. per liter and the electrocardiogram showed slight flattening of T waves. By 17 hours after initiation of therapy the patient was active and started taking a soft diet well. The serum HCO_3 was 34.6 meq. per liter, the serum K 3.1 meq. per liter, and the T waves in the ECG were flattened and broad. By 41 hours all chemical values and the ECG were within normal limits.

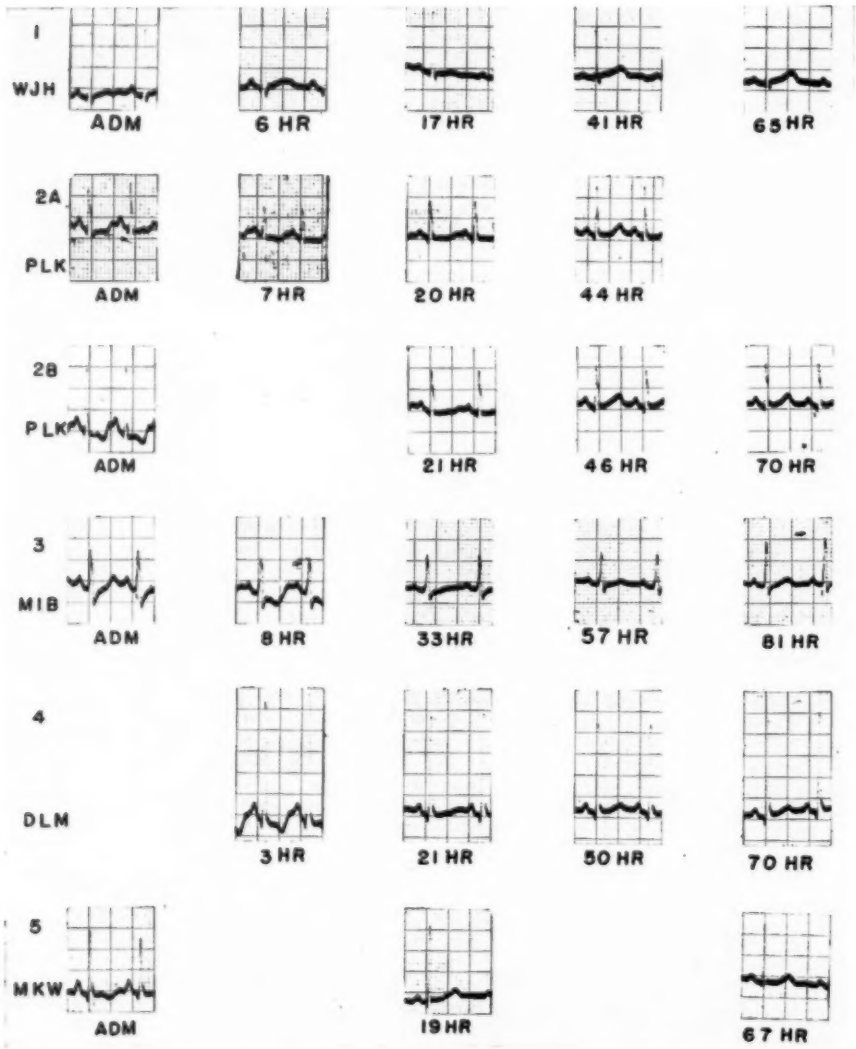


Fig. 1.—Serial electrocardiograms of patients treated without added potassium (Standard L_2).

CASE 2.—P. L. K., a 4-year-old white female, was first admitted on March 22, 1951, with a history of high fever for one day, followed by two months of polydipsia, polyphagia, and polyuria. During this time the child lost approximately twenty pounds. The night prior to admittance the patient became lethargic, developed rapid respirations, and vomited repeatedly. By morning the child was difficult to arouse and failed to recognize her parents.

Physical examination revealed a semicomatose, markedly malnourished, dehydrated child with Kussmaul respirations. Both tympanic membranes were injected and dull, and the liver was tender to palpation. The serum HCO_3 was 5.8 meq. per liter, and the serum true glucose was 575 mg. per 100 ml. (Table I). An electrocardiogram at this time revealed prolongation of the RS-T segment in all leads, slightly depressed RS-T segment in L_2, aV_F, V_5 and V_6, and elevated RS-T segment in aV_R (Fig. 1).

The child received 1/6 molar sodium lactate, hypotonic Ringer's solution, and regular insulin. Seven hours after the initial therapy the blood chemical findings were almost normal. An electrocardiogram at this time revealed some flattening of the T waves in L_1, L_2, and the augmented unipolar limb leads. The RS-T segment was prolonged in all leads and slightly depressed in L_2. At this time she was alert and taking oral fluids, and the electrocardiogram the next morning was within normal limits. It will be noted that the serum K values were all within normal limits.

After discharge, the patient did well until one month prior to the second admittance at which time she developed frequent headaches and constipation. The diabetes was poorly controlled during this month. Six days prior to the second entry she developed fever which disappeared in a few days, and about twenty-four hours before entry to the hospital she began to vomit. She received 30 units of regular insulin on the morning of admittance.

Physical examination revealed a fairly well-developed, lethargic child. The respirations were rapid and deep. There was moderate dehydration, and she had an area of cellulitis over the left lateral malleolus. The serum HCO_3 was 6.1 meq. per liter, and the serum true glucose was 351 mg. per 100 ml. (Table I). An electrocardiogram revealed a tachycardia of 160 per minute, and the RS-T segment was prolonged in all leads and depressed in L_2, L_3, aV_F, V_{3-6} (Fig. 1).

The patient received 1/6 molar sodium lactate, hypotonic Ringer's solution, and regular insulin. The serum HCO_3, twenty-one hours later, was 20.8 meq. per liter. At this time the child's respirations were normal, and she was taking oral fluids. Twenty hours after admittance the urine was free of ketone bodies. The electrocardiogram showed flattening of the T wave in all limb leads and was diphasic in V_5. The following morning the tracing was within normal limits and remained so until discharge. The serum K values during this hospitalization showed only minor deviations.

CASE 3.—M. I. B., an 11-year-old white female, was admitted with a history of increasing lethargy, marked weight loss, polydipsia, and polyuria of one month's duration. Twelve hours prior to admittance her respirations became deep and rapid, and she vomited several times. Six to eight hours before entry she became unconscious.

Physical examination revealed a markedly emaciated, dehydrated, semicomatose child. An acetone odor on her breath was very evident. The serum HCO_3 was 6.9 meq. per liter, and the serum true glucose was 1,025 mg. per 100 ml. (Table I). The urine analysis revealed 6 per cent sugar and strongly positive $FeCl_3$ and Rothera tests. An electrocardiogram at this time revealed depression of the RS-T segment in L_2, L_3, and aV_F and an

TABLE I. SERIAL BLOOD CHEMICAL FINDINGS OF PATIENTS TREATED WITHOUT ADDED POTASSIUM

NAME	TIME	HCO_3 MEQ./L.	CL MEQ./L.	NA MEQ./L.	K MEQ./KG.	CA MG./100 ML.	PROTEIN GM./100 ML.	A/G GM./100 ML.	GLUCOSE MG./100 ML.
1. W. J. H.	Adm.	9.4	90.0	142.0	5.1	11.6			435.0
	6 hr.	17.4	87.0	139.2	4.7	11.6	6.46	3.99/2.47	226.0
	17 hr.	34.6	93.0	147.2	3.1	10.3			86.0
	41 hr.	30.1	96.0	146.0	5.0	10.6			286.0
	65 hr.	27.0	93.0	146.8	4.4				410.0
	89 hr.	25.0	92.0	139.2	5.7	12.2			410.0
2. P. L. K.	Adm.	5.8	105.0	136.0	5.4				575.0
A	7 hr.	19.6	102.0	----	4.7				390.0
	20 hr.	—	----	137.0	4.6				
	44 hr.	—	----	142.0	4.3				
B	Adm.	6.1	105.2	152.0	3.6				351.0
	7 hr.	20.8	----	----	--				47.2
	21 hr.	—	----	141.8	3.1				258.0
	46 hr.	—	----	144.5	4.3				
	70 hr.	—	----	142.6	4.3				
3. M. I. B.	Adm.	6.9	89.6	119.0	5.6	---			1,025.0
	8 hr.	24.4	91.4	139.0	3.0	12.0			351.0
	33 hr.	—	----	137.0	2.8	---			----
	57 hr.	—	----	138.0	3.0	---			----
	81 hr.	—	----	140.0	4.3	---			----
	105 hr.	28.1	94.4	139.0	4.3	10.3	4.94	2.95/1.99	251.0
4. D. L. M.	Adm.	9.6	95.0	129.0	5.3				375.0
	12 hr.	—	----	134.0	4.2				----
	21 hr.	33.8	86.6	137.0	3.6				166.0
	45 hr.	—	----	142.0	4.3				----
	69 hr.	—	----	134.0	5.0				----
	93 hr.	—	----	136.0	5.3				----
5. M. K. W.	Adm.	12.4	----	140.0	4.0				141.0
	19 hr.	29.6	----	139.0	3.5				139.0
	67 hr.	—	----	139.0	3.5				----
	91 hr.	—	----	142.0	4.1				----
6. D. J. K.	Adm.	8.9	96.0	137.2	4.1	9.8			535.0
	8 hr.	27.9	90.0	145.2	3.0	9.5			----
	20 hr.	31.6	92.0	144.2	2.5	8.8			131.0
	45 hr.	29.8	99.0	145.0	3.9	---			----
	92 hr.	25.6	99.0	145.2	4.2	10.6			197.0
	117 hr.	—	----	146.0	4.4	---			----
7. M. A.	Adm.	4.9	112.0	137.1	3.1	---			360.0
	6 hr.	11.0	109.0	151.4	1.8	---			55.7
	29 hr.	26.7	100.0	137.9	2.4	9.2			51.3
	54 hr.	28.5	94.0	142.0	4.4	---			----

8. B. G. S.	Adm.	11.7	92.8	----	--	---			448.9
	8 hr.	22.4	104.0	142.5	4.5	11.2			175.0
	31 hr.	24.4	104.0	136.8	4.1				71.0
9. R. L. S.	Adm.	3.6	86.0	134.0	4.5	---	6.24	3.95/2.29	699.3
	6 hr.	16.5	92.0	136.9	3.3	12.7	---	----	185.0
	17 hr.	30.5	----	139.1	3.2	11.0	---	----	133.0
	39 hr.	37.6	90.8	140.0	3.1	11.2	---	----	214.0
	62 hr.	33.2	95.0	135.0	4.1	11.0	---	----	343.0
	86 hr.	29.8	90.0	141.9	5.2	10.9	6.07	3.23/2.84	----
10. W. L.	Adm.	7.3	93.0	128.4	4.0	---	---	----	405.0
	10 hr.	16.7	93.0	133.8	3.1	---	---	----	----
	36 hr.	—	----	136.2	3.2	---	---	----	173.5
	60 hr.	—	96.0	136.7	3.3	---	---	----	----
	102 hr.	—	----	138.2	3.9	---	---	----	114.5
11. R. W.	Adm.	8.8	93.0	----	--	11.4	---	----	350.0
	9 hr.	35.8	94.0	134.0	3.2	---	4.91	2.32/2.59	280.0
	31 hr.	36.7	100.0	144.0	3.7	10.3	---	----	118.5
	88 hr.	24.4	100.0	139.8	4.4	11.2	---	----	254.0
	112 hr.	28.7	98.0	133.0	4.4	9.8	---	----	365.0
12. R. J. G.	Adm.	5.4	106.0	132.9	4.7	---	---	----	358.0
	6 hr.	20.2	102.0	141.0	3.0	---	---	----	165.0
	12 hr.	24.4	94.0	141.6	3.4	---	---	----	192.0
13. C. W.	Adm.	6.9	----	----	--	---	---	----	545.0
	9 hr.	14.1	93.0	135.2	4.6	---	---	----	455.0
	31 hr.	32.8	91.0	----	--	---	---	----	48.0
	61 hr.	31.7	97.0	129.8	4.2	---	---	----	----
	80 hr.	28.2	104.0	133.2	4.5	10.7	---	----	----
14. T. W. S.	Adm.	10.9	96.0	135.2	4.1	---	---	----	502.0
	7 hr.	—	----	140.0	2.2	---	---	----	70.5
	11 hr.	—	----	141.2	2.4	---	---	----	85.7
	17 hr.	28.9	92.0	139.0	--	---	---	----	----
	85 hr.	—	----	136.2	4.0	---	---	----	----
15. B. S. N.	Adm.	9.9	101.4	135.2	4.4	---	---	----	167.0
	2 hr.	—	----	139.0	3.2	---	---	----	150.0
	5 hr.	26.5	84.4	135.0	2.8	---	---	----	109.0
	13 hr.	—	----	132.0	2.6	---	---	----	133.0
	39 hr.	—	----	141.7	3.2	---	---	----	----
	62 hr.	33.3	90.0	133.2	3.9	---	---	----	----

elevated RS-T segment in aV_R and aV_L (Fig. 1). She received 1/6 molar sodium lactate, hypotonic Ringer's solution, and regular insulin in the usual manner.

Within seven hours the patient responded and took a small amount of oral fluids. An electrocardiogram showed flattening of the T wave in the limb leads and depression of the RS-T segment in all leads except aV_R and aV_L. At this time she received 20 units of regular insulin and lactate Ringer's solution subcutaneously, and during the night she was given lactate Ringer's solution plus 10 per cent glucose in distilled water and regular insulin.

Twenty-four hours after admittance the Rothera and $FeCl_3$ tests became negative. About thirty-six hours later she started eating, although she was slightly lethargic. The electrocardiogram was within normal limits except for slight flattening of T wave in L_2. The patient was discharged on April 10, 1951, in good control. The serum K was 5.6 meq. per liter upon admittance and did drop to 2.8 meq. per liter at 33 hours, but at that time she was awake enough to start eating and no manifestations of hypokaliemia were noted.

CASE 4.—D. L. M., a 10-year-old white female, had been known to have diabetes for over one year. Four days prior to admittance she developed marked injection of the right conjunctiva, and two days before entry the patient started to vomit, took little food, and the insulin dosage was reduced.

Physical examination revealed a semicomatose, dehydrated child with deep, pauseless respirations. The upper and lower eyelids on the right were swollen, and a hordeolum of the upper lid was present. The serum HCO_3 was 9.6 meq. per liter, and the serum true glucose was 375 mg. per 100 ml. (Table I). She received regular insulin, 1/6 molar sodium lactate and hypotonic Ringer's solution. During the administration of the fluids, an electrocardiogram was obtained which showed flattening of the T wave in L_1 and aV_R and inversion in L_2, L_3, aV_F, and $V_{5,6}$ (Fig. 1).

Nine hours after admittance the child was alert and took oral feedings. At twenty-one hours the electrocardiogram showed flattening of the T waves in L_1, L_2, aV_R, and questionable flattening of V_5, at which time the serum K was 3.5 meq. per liter. At this time the Rothera and $FeCl_3$ tests became negative, and the following day the electrocardiogram was within normal limits.

CASE 5.—M. K. W., a 12-year-old white female, was a known diabetic for two and one-half years. About two and one-half weeks prior to admittance she developed a sore throat which lasted three days and was accompanied by a marked glycosuria. The night prior to entry she complained of abdominal pain and vomited frequently. She received the usual insulin dosage on the morning of admittance. Physical examination on entry revealed a moderately injected throat and a small infected ulcer over the left lateral malleolus. The serum HCO_3 was 12.4 meq. per liter, and serum true glucose was 141 mg. per 100 ml. (Table I). An electrocardiogram revealed flattened T wave with an inverted T in L_2 and aV_F and upright T wave in aV_R. The RS-T segment was slightly depressed in L_2, L_3, and aV_F. The P waves were markedly peaked in all limbs leads (Fig. 1).

The patient received the usual treatment and seven hours later was alert and ate well. An electrocardiogram at nineteen hours was within normal limits and remained so, although the serum K level dropped to 3.5 meq. per liter at 19 and 67 hours. The remainder of the hospital stay was uneventful.

CASE 6.—D. J. K., a 9-year-old white female, was admitted with a history of diabetes mellitus of twenty-two months' duration. Diabetic control was poor because of irregular insulin

administration. Five days prior to admittance symptoms of an upper respiratory infection developed followed two days later by vomiting, diarrhea, and decreased food intake.

Upon entry to the hospital the child was lethargic and moderately dehydrated. The respirations were deep but not rapid. The pharynx was mildly injected, and the liver was palpated 3 cm. below the costal margin. The serum HCO_3 was 8.9 meq. per liter, and the serum true glucose was 535 mg. per 100 ml. (Table I). Urinalysis revealed 5 per cent sugar and positive $FeCl_3$ and Rothera tests. The electrocardiogram was within normal limits (Fig. 2).

Eight hours after the initiation of routine therapy the patient was alert, and the respirations were normal. Nineteen hours after admittance the patient started taking oral feedings. At this time the serum true glucose was 131 mg. per 100 ml., the serum HCO_3 31.6 meq. per liter, and the serum potassium 2.5 meq. per liter. The electrocardiogram revealed prolongation of the RS-T segment in all leads and depression in $V_{3,5}$, and the T waves were flattened to inverted in all leads (Fig. 2). The blood chemical findings were essentially normal by 45 hours, and the electrocardiogram was within normal limits, but showed slight flattening of the T waves in all leads on the next two days.

CASE 7.—M. A., an 18-month-old white female, was admitted to the hospital with a history of lethargy, polyuria, and polydipsia, and poor food intake of two to three months' duration. Four days prior to admittance the parents noted the onset of fever and rapid deep respirations.

Physical examination revealed a severely dehydrated infant with typical Kussmaul breathing. The serum HCO_3 was 4.9 meq. per liter, and the serum true glucose was 360 mg. per 100 ml. (Table I). The urinalysis showed 4 plus sugar. The usual treatment was started.

Six hours after admittance the patient was still hyperventilating and dehydrated, but was improved. The serum HCO_3 was 11.0 meq. per liter, and the serum K level was 1.8 meq. per liter. The T waves were flattened to diphasic in all the leads, and the RS-T segment was depressed in V_{1-5} (Fig. 2). At twelve hours the patient was markedly improved and started taking oral feedings. About twenty-four hours after the initial treatment was started, the urine was free of ketone bodies. At thirty hours the infant was alert and was started on a diabetic diet. The serum HCO_3 was 26.7 meq. per liter. The electrocardiogram at this time revealed flattening of the T waves in all leads and the next morning was within normal limits. Despite the severe drop in serum K, this patient did not show any clinical evidence of hypokaliemia.

CASE 8.—B. G. S., a 10-year-old white male, was a known diabetic for over two years. He was well until two days prior to admittance, at which time he developed a sore throat. The child was given symptomatic treatment, but on the day of entry started vomiting.

Physical examination revealed moderate dehydration and injection of the tympanic membranes and mucous membranes. The respirations were normal. The serum HCO_3 was 11.7 meq. per liter, and the serum true glucose was 448.9 mg. per 100 ml. (Table I). The urinary sugar was 4 per cent, and the Rothera and $FeCl_3$ tests were strongly positive. The patient was given 15 ml. per kilogram of 1/6 molar sodium lactate, 20 ml. per kilogram of Ringer's solution intravenously, and 2 units per kilogram of regular insulin. Eight hours later the serum HCO_3 was 22.4 meq. per liter. The electrocardiogram showed minimal flattening of the T waves in all leads (Fig. 2). The patient was started on a liquid diet which was retained. The urine was free of ketone bodies after 24 hours. The ECG taken

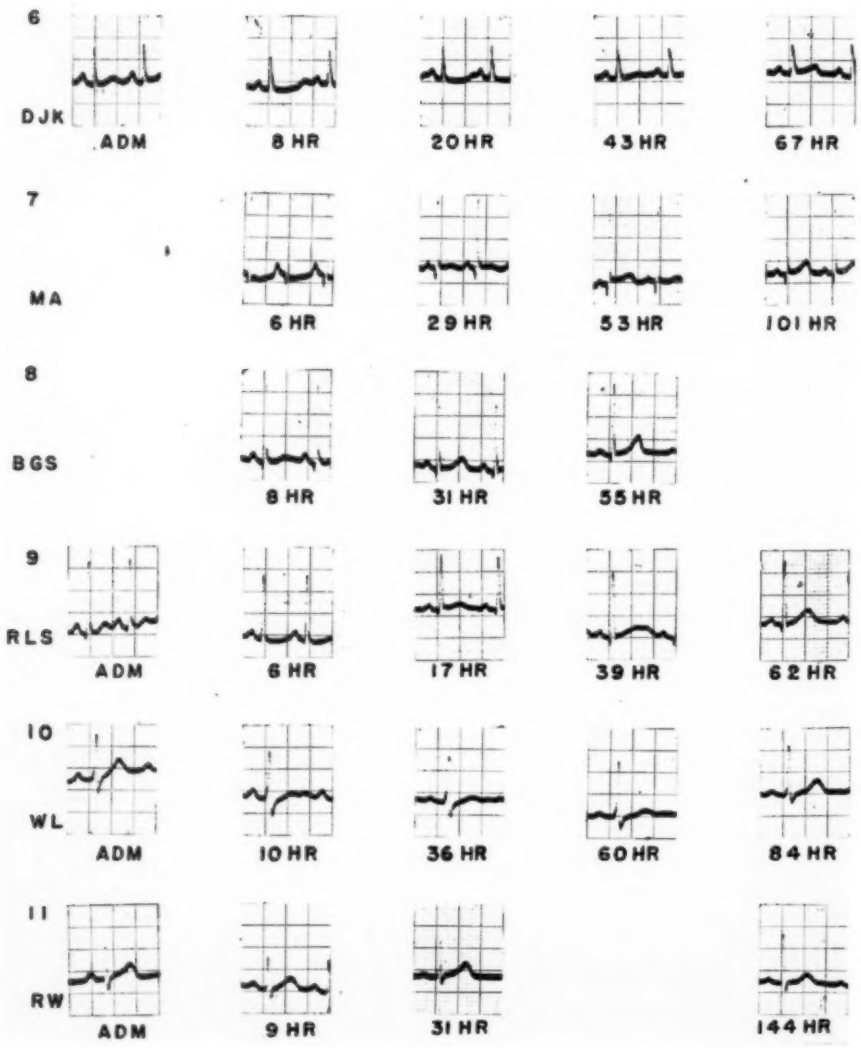


Fig. 2.—Serial electrocardiograms of patients treated without added potassium (Standard L_6).

thirty hours after admittance was within normal limits.

CASE 9.—R. L. S., a 13-year-old white male, was a known diabetic for three years, who for several months prior to admittance had been losing weight and under poor control. Twenty-four hours prior to entry the patient started vomiting and eight hours later the $FeCl_3$ test was noted to be positive, at which time he received 35 units of protamine zinc insulin and 35 units of regular insulin. Four to five hours later the patient was unresponsive and breathing rapidly and deeply.

Physical examination revealed a comatose, dehydrated child with Kussmaul breathing. The tympanic membranes were dull and injected and his abdomen was distended. The serum HCO_3 was 3.6 meq. per liter (Table I). One unit of regular insulin per kilogram was given subcutaneously, 30 ml. per kilogram of 1/6 molar Na lactate intravenously, and 30 ml. per kilogram of 1/6 molar Na lactate plus 30 ml. per kilogram of hypotonic Ringer's solution were started subcutaneously. The electrocardiogram taken shortly after starting therapy was within normal limits except for some depression of the RS-T segment (Fig. 2).

Six hours after the initiation of therapy the serum HCO_3 was 16.5 meq. per liter, and serum K was 3.3 meq. per liter. The electrocardiogram at this time showed broad, flat T waves. Shortly after these studies the patient was responsive and started taking orange juice orally. At 39 hours the serum HCO_3 was 37.6 meq. per liter, and serum chlorides were 90.8 meq. per liter, but no signs of alkalosis were present. The serum K was 3.1 meq. per liter, and the electrocardiogram revealed broad T waves, but the changes were definitely less marked than in the earlier tracing. The blood chemical values and electrocardiogram were entirely normal by the fourth day.

CASE 10.—W. L., an 11-year-old Negro male, was known to have diabetes mellitus for eight months during which time he was controlled by diet and 10 units regular insulin and 10 units protamine zinc insulin per day. For seven to ten days the child did not adhere to the diet and the day before entry developed signs of upper respiratory infection. The next day vomiting started and the child rapidly became stuporous. Six hours before being brought to the hospital, respirations were noted to be rapid and deep.

Physical examination revealed a semicomatose, dehydrated child with Kussmaul breathing. Temperature was 38.2° C. The nasal mucosa was edematous and injected, as was the pharynx. Urine analysis showed 4 plus sugar and a strongly positive $FeCl_3$ test. The serum HCO_3 was 7.3 meq. per liter and the serum true glucose was 405 mg. per 100 ml. (Table I). An electrocardiogram at this time was within normal limits (Fig. 2).

Therapy was started which included 1 unit per kilogram of regular insulin (had received 20 units of insulin in the morning), 30 ml. per kilogram of 1/6 M Na lactate intravenously, and 30 ml. 1/6 M Na lactate and 40 ml. per kilogram of hypotonic Ringer's solution subcutaneously. Ten hours later the serum HCO_3 was 16.7 meq. per liter, and the serum K was 3.1 meq. per liter. The electrocardiogram revealed broadening of the T waves and slight depression of the RS-T segments, but the patient was alert and ate a soft diet well. Although the patient was clinically well, the serum K and electrocardiogram did not return to normal until 102 hours and 84 hours, respectively, after entry.

CASE 11.—R. W., a 13-year-old white male, was a known diabetic for three years and was well regulated by diet plus 60 units of regular insulin and 60 units of PZI per day. Four days prior to admittance the patient stopped taking his insulin. Twenty-four hours before entering the hospital he became lethargic and over the next

ten to twelve hours became semicomatose.

Physical examination revealed a semicomatose child who intermittently complained of pain in his arms and legs. The respirations were rapid and signs of dehydration were present. The pharynx and tympanic membranes were injected. The abdomen was tense but no organs were palpable. The urine was positive for sugar and acetone. The serum HCO_3 was 8.8 meq. per liter, and the serum true glucose was 350 mg. per 100 ml. (Table I). The electrocardiogram was within normal limits and remained unchanged during recovery (Fig. 2).

Therapy of 2 units per kilogram of regular insulin plus the "routine" fluids were started. Recovery was rapid with the patient eating a soft breakfast seven and one-half hours later. The lowest serum K was 3.2 meq. per liter at 9 hours, which returned to normal by 31 hours. Although mild overriding of the serum HCO_3 occurred, no signs of alkalosis were present.

CASE 12.—R. J. G., a 4-year-old Negro female, had measles one month before entering St. Louis Children's Hospital. Following this illness, polyphagia developed. Four to five days prior to admittance, polyuria and enuresis developed, and shortly thereafter, signs of an upper respiratory infection manifested by sore throat and nasal discharge became apparent. Twelve hours before entering the hospital the child developed vomiting, listlessness, and tachypnea which rapidly became worse.

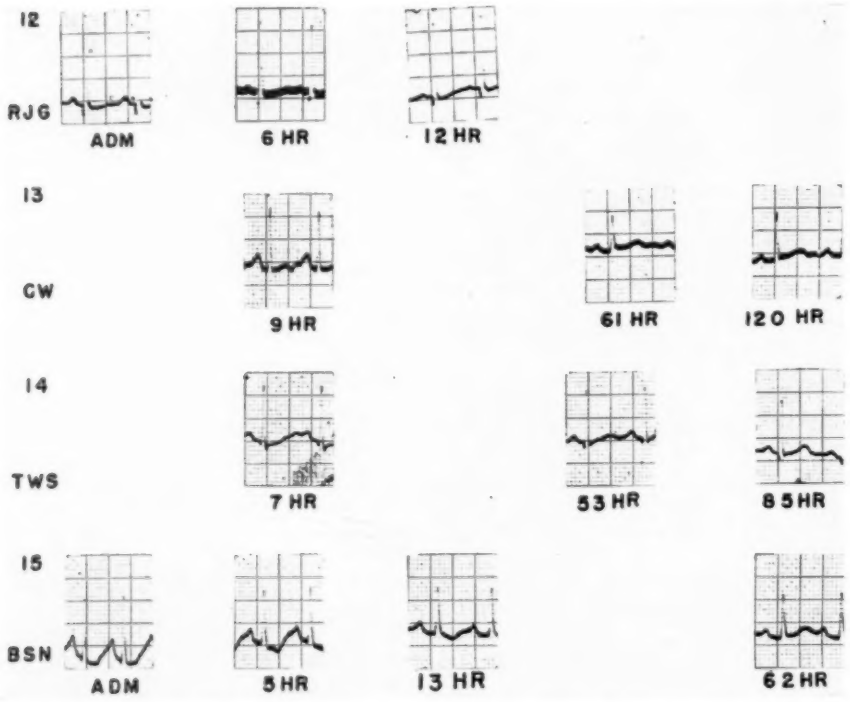


Fig. 3.—Serial electrocardiograms of patients treated without added potassium (Standard L_2).

Physical examination revealed a malnourished, semicomatose child with typical Kussmaul breathing, and a strong odor of acetone could readily be detected on her breath. Clinical signs of dehydration were present. The remainder of the examination was negative except for injection of the pharynx. Urinalysis revealed the presence of sugar and acetone. The serum HCO_3 was 5.4 meq. per liter, and the serum true glucose 358 mg. per 100 ml. (Table I). The electrocardiogram was within normal limits except for flattening of the T_2. (Fig. 3.)

The patient was given 2 units per kilogram of regular insulin and 30 ml. per kilogram of 1/6 molar sodium lactate intravenously along with 30 ml. per kilogram of 1/6 molar sodium lactate and 40 ml. per kilogram of Ringer's solution subcutaneously. Recovery was exceptionally rapid, and four hours after admittance the child was asking for food. Six hours after starting the initial therapy, the serum HCO_3 was 20.2 meq. per liter and the serum K was 3.0 meq. per liter, which returned to 3.4 meq. per liter by 12 hours.

CASE 13.—C. W., a 15-year-old Negro female, who was a known diabetic for two years, was admitted to St. Louis Children's Hospital because of listlessness, anorexia, and lethargy of thirty-six hours' duration. On the morning of entry the patient took 25 units of regular insulin and 25 units of P.Z.I., but during the day she refused all feedings. When she was first seen in the emergency room, hypoglycemia was considered, and Adrenalin was administered with only temporary relief following which definite hyperventilation was noted.

Physical examination revealed an acutely ill, undernourished, obtunded child who was moderately dehydrated. The temperature was 38° C. The tympanic membranes and pharynx were injected. The respirations were deep and pauseless, but examination of the heart and lungs was negative. A fluctuant abscess involving the posterior portion of the vulva and the perirectal area was found. The serum HCO_3 was 6.9 meq. per liter, and the serum true glucose was 545 mg. per 100 ml. (Table I). Regular insulin, 2 units per kilogram, was given followed by intravenous and subcutaneous fluids totaling 65 ml. per kilogram of 1/6 molar sodium lactate and 55 ml. per kilogram of hypotonic Ringer's solution. The perineal abscess was incised and drained and a culture of the purulent material grew out a budding yeast.

Nine hours after entry the serum HCO_3 was 14.1 meq. per liter, serum Na was 135.2 meq. per liter, and serum K was 4.6 meq. per liter. The electrocardiogram at this time revealed slight flattening of the T waves (Fig. 3). Recovery was rapid and the patient became afebrile after forty-eight hours. The electrocardiogram taken at 60 hours revealed flattened T waves with prominent U waves, although the serum K never dropped below 4.2 meq. per liter.

CASE 14.—T. W. S., a 5-year-old white male, was in good health until two and one-half months prior to entering the hospital. During this time polyuria, polydipsia, decreasing appetite, and weight loss developed. Over the latter part of this period, lethargy and easy fatigability were noted.

Physical examination revealed a well-developed, somewhat thin child who was extremely lethargic. Respirations were rapid and acetone could be detected on his breath. Dehydration was moderate, but the remainder of the examination was normal. Urinalysis revealed 4 plus sugar and a strongly positive $FeCl_3$ test. The serum HCO_3 was 10.9 meq. per liter, and the serum true glucose was 502 mg. per 100 ml. (Table I).

The child was given 2 units per kilogram of regular insulin and 30 ml. per kilogram of 1/6 molar sodium lactate intravenously and 15 ml. per kilogram of 1/6 molar sodium lactate

plus 20 ml. per kilogram of hypotonic Ringer's solution subcutaneously.

Seven hours later the serum K had dropped from 4.1 to 2.2 meq. per liter and the electrocardiogram revealed depression of the RS-T segment in the limb leads and broad T waves. The electrocardiogram and blood chemistries rapidly returned to normal by 53 hours, except for slight T-wave changes.

CASE 15.—B. S. N., an 8-year-old white female, was well until five to six weeks prior to admittance, when she was noted to develop enuresis, polyuria, polydipsia, and polyphagia which progressively increased in intensity. During the last two weeks weight loss was noted. Lethargy and listlessness increased and rapid respirations developed. The child was admitted to another hospital where a tentative diagnosis of tuberculous meningitis was made and 250 ml. of 10 per cent glucose in saline was given. Urinalysis revealed 4 plus sugar and strongly positive $FeCl_3$ test. Forty units of regular insulin were given on two occasions two hours apart and the child was referred to St. Louis Children's Hospital.

Physical examination revealed an emaciated child who was markedly dehydrated and semicomatose. The respirations were deep and pauseless. The remainder of the examination was negative. The serum HCO_3 was 9.9 meq. per liter, and the serum true glucose was 167 mg. per 100 ml. (Table I). The electrocardiogram at this time revealed sinus tachycardia, diphasic T waves, and depression of the RS-T segments (Fig. 3). Since the child had already received insulin, only 1 unit per kilogram of regular insulin was administered subcutaneously. Sodium lactate and hypotonic Ringer's solution were given as usual. Five hours later the child started taking orange juice at which time the serum K was 2.8 meq. per liter and the ECG was the same as the initial tracing, except for more severe RS-T segment depression. At 13 hours after entry the serum K was 2.6 meq. per liter and the ECG revealed marked flattening of the T waves, but the RS-T segments were not depressed. By 62 hours the blood chemistries and ECG were within normal limits except for a serum Cl of 90.0 meq. per liter and serum HCO_3 of 33.3 meq. per liter.

GROUP II

CASE 1K.—V. J. S., a 13-year-old white female diabetic of six years' duration, was well until five days prior to admittance. At that time, the patient developed glycosuria and fatigability and she was given an additional 10 units of regular insulin in the late afternoon (18 regular insulin and 18 P.Z.I. insulin given subcutaneously before breakfast). Twenty-four hours later, upon returning from school, rapid respirations were noted, and the urine examination revealed a severe glycosuria and a positive $FeCl_3$ test. Three days prior to entry the child developed headache and low back pain and, in spite of an increase in the morning insulin and an additional 10 units of regular insulin before supper, she became progressively worse.

Physical examination revealed a very lethargic, disoriented, acutely ill child who was well developed, but poorly nourished (admission weight 43.9 kilograms). The skin and mucous membranes were dry and the face was flushed. The tympanic membranes and pharynx were injected. The respirations were deep and rapid. The serum HCO_3 was 6.4 meq. per liter, and the serum true glucose was 435 mg. per 100 ml. (Table II). Urine examination revealed 4 per cent sugar and the presence of acetone and diacetic acid. She was given 46 units of regular insulin, 56 ml. per kilogram of 1/6 molar sodium lactate, 3.7 ml. per kilogram of 1/6 molar potassium lactate, and 40 ml. per kilogram hypotonic Ringer's solution. The electrocardiogram before therapy revealed some flattening of T waves in L_2 (Fig. 4). Six hours after entry the serum HCO_3 was 12.1 meq. per liter, and the elec-

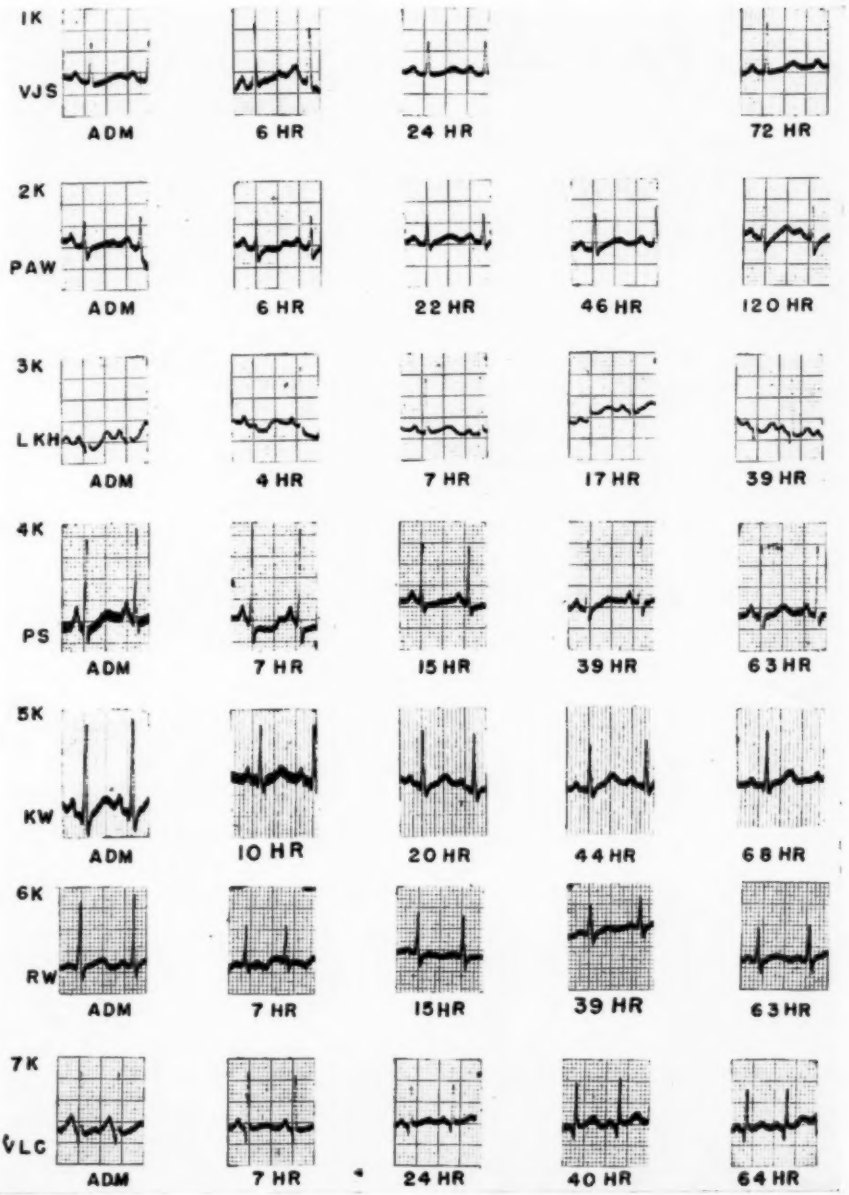


Fig. 4.—Serial electrocardiograms of patients treated with added potassium (Standard L_2).

TABLE II. SERIAL BLOOD CHEMICAL FINDINGS OF PATIENTS TREATED WITH ADDED POTASSIUM

NAME	TIME	HCO_3 MEQ./L.	CL MEQ./L.	NA MEQ./L.	K MEQ./KG.	CA MG./100 ML.	PROTEIN GM./100 ML.	A/G GM./100 ML.	GLUCOSE MG./100 ML.
1K. V. J. S.	Adm.	6.4	104.0	130.8	4.8	---	----	----	435.0
	6 hr.	12.1	97.0	133.6	2.7	---	----	----	232.0
	11 hr.	20.5	----	----	--	---	----	----	262.5
	24 hr.	22.0	91.0	134.1	2.6	---	----	----	191.0
	47 hr.	---	----	137.0	2.8	---	----	----	338.0
	72 hr.	---	100.0	138.6	3.1	10.4	----	----	326.0
	96 hr.	---	----	147.2	3.6	---	----	----	----
	120 hr.	---	----	139.5	4.6	---	----	----	63.8
2K. P. A. W.	Adm.	3.4	95.2	134.0	4.9	10.2	----	----	520.0
	6 hr.	---	----	134.0	3.5	---	----	----	----
	8 hr.	11.6	97.0	134.5	3.4	---	----	----	60.0
	22 hr.	22.6	92.0	131.1	4.7	10.0	----	----	----
	46 hr.	---	----	130.5	4.0	---	----	----	----
	70 hr.	---	----	132.0	4.0	---	----	----	----
3K. L. K. H.	Adm.	5.4	102.0	134.2	3.8	---	----	----	354.0
	7 hr.	10.2	98.4	140.2	3.1	11.2	----	----	88.0
	17 hr.	20.6	98.0	134.2	3.5	9.6	----	----	75.0
	39 hr.	29.2	100.0	139.0	3.5	11.9	----	----	97.5
	63 hr.	29.1	95.4	136.3	4.6	---	----	----	254.0
4K. P. S.	Adm.	9.5	96.0	121.5	5.8	---	----	----	520.0
	7 hr.	17.6	97.0	128.5	3.5	---	----	----	140.0
	15 hr.	23.1	98.0	133.5	3.3	10.0	----	----	----
	39 hr.	29.2	86.0	132.5	4.4	---	----	----	----
	63 hr.	---	----	133.5	3.5	---	----	----	----
	87 hr.	---	----	133.0	4.3	---	----	----	----
5K. K. L. W.	Adm.	12.7	97.0	135.8	4.7	12.5	----	----	450.0
	11 hr.	---	103.0	135.8	4.1	10.1	----	----	----
	20 hr.	21.9	100.0	140.2	4.2	10.6	----	----	66.0
	44 hr.	25.5	97.0	132.9	4.6	10.5	----	----	354.0
6K. R. W.	Adm.	8.5	102.0	134.2	5.1	12.0	----	----	405.0
	7 hr.	22.0	99.0	139.5	4.3	10.5	----	----	174.0
	15 hr.	30.3	91.0	131.6	3.1	8.8	----	----	206.0
	39 hr.	30.4	97.0	135.5	3.5	9.8	----	----	183.0
	63 hr.	---	----	136.8	3.8	9.5	----	----	----
	111 hr.	21.6	94.0	133.5	4.3	---	----	----	----
7K. V. L. C.	Adm.	8.9	96.0	133.7	4.6	---	----	----	417.0
	7 hr.	25.0	101.0	136.8	3.4	---	----	----	79.5
	16 hr.	27.5	94.0	134.8	3.5	10.4	----	----	35.0
	24 hr.	---	----	133.5	4.0	---	----	----	120.0
	44 hr.	28.4	93.0	132.0	3.8	---	----	----	200.0
	68 hr.	---	----	134.8	3.9	---	----	----	----

trocardiogram at this time revealed broad T waves in all leads. Two hours later the patient started taking orange juice orally and by 24 hours the child was alert and eating. At this time the serum HCO_3 was 22.0 meq. per liter, and the electrocardiogram was within normal limits. The serum K level was normal upon admittance, but dropped to 2.6 meq. per liter at 24 hours and returned to 3.6 meq. per liter by 96 hours. In spite of a slightly lower serum potassium level the patient was up and active about the ward by 48 hours.

CASE 2K.—P. A. W., a 12-year-old white male, was first treated at St. Louis Children's Hospital after having diabetes for five years. The child had been regulated on a low fat diet and regular insulin three times a day. Four days prior to admittance, while at camp, the child developed an abscess on the side of his nose which progressively became worse. On the morning prior to entry the child did not eat breakfast or take his insulin and shortly afterward became comatose.

Physical examination revealed an acutely ill, comatose child who was poorly developed, and whose respirations were Kussmaul in type. There was evidence of severe dehydration and a large fluctuant abscess on the left side of the nose and face was present.

The serum HCO_3 was 3.4 meq. per liter, and the serum true glucose was 520 mg. per 100 ml. (Table II). Urinalysis revealed 4 per cent glucose and a positive $FeCl_3$ and Rothera tests. The initial electrocardiogram revealed broad T waves in L_1, V_2, V_3, V_4, and flat T waves in all leads except $V_{2, 3, 4}$. The RS-T segments were slightly depressed in L_1, L_2, aV_F. (Fig. 4.)

Treatment was started with 2 units per kilogram of regular insulin, 30 ml. per kilogram of 1/6 molar sodium lactate and 20 ml. per kilogram of hypotonic Ringer's solution intravenously, and 30 ml. per kilogram of 1/6 molar potassium lactate and 20 ml. per kilogram of hypotonic Ringer's solution subcutaneously. Hot packs to the nose and parenteral antibiotics were started. Eight hours later the HCO_3 was 11.6 meq. per liter and the serum K level was 3.4 meq. per liter. Electrocardiograms at 3½ and 8 hours revealed flat T waves with prominent U waves in all leads, and the RS-T segments in L_2, L_3, and aV_F were slightly depressed. Twelve hours after entry, the patient was alert, and at that time the electrocardiogram revealed flattened T waves. By 20 hours he was taking a soft diabetic diet, and the blood chemistries were within normal limits except for a serum sodium of 131.1 meq. per liter, which remained low for at least 70 hours. The electrocardiogram at 46 hours still showed broad, flat T waves in all leads. Seven days after admittance the tracing was still suspicious, and the final electrocardiogram taken on the twenty-second day was essentially unchanged. This may be considered as the baseline electrocardiogram for this patient, since the initial electrocardiogram was essentially the same as the ones taken on the twenty-second day.

CASE 3K.—L. K. H., a 3-year-old white female, was admitted with a history of easy fatigability for some time. One week prior to entry she developed polyuria and polydipsia. Twenty-four hours before entering the hospital the parents noted the onset of rapid, deep respiration.

Physical examination revealed an acutely ill, dehydrated, semicomatose patient, who appeared fairly well nourished. Respirations were rapid and deep. The tonsils were moderately enlarged and injected and there was a mucopurulent nasal discharge. The liver was palpated 2 cm. below the costal margin. The serum HCO_3 was 5.4 meq. per liter, the serum true glucose 354 mg. per 100 ml., and the serum K 3.8 meq. per liter (Table II). The initial electrocardiogram was within normal limits except for a tachycardia of 136 per minute (Fig. 4). Two units per kilogram of regular insulin were given subcutaneously and parenteral fluids were started. A total of 78 ml. per kilogram of 1/6 molar Na lactate, 8 ml. per kilogram of

hypotonic Ringer's, and 49 ml. per kilogram of distilled water with 2.4 Gm. (2.2 meq. per kilogram) of KCl were given. Seven hours after starting therapy the serum HCO_3 was 10.2 meq. per liter and the serum K 3.1 meq. per liter. The electrocardiogram at this time revealed some flattening of the T waves. Ten hours later the child was able to eat a soft diabetic diet. The serum HCO_3 at that time was 20.6 meq. per liter, and the serum K was 3.5 meq. per liter. The electrocardiogram at this time was essentially the same as the previous tracing. Twenty-four hours later the electrocardiogram was within normal limits and the blood chemical findings were normal except for the serum K which remained at 3.5 meq. per liter and did not reach normal levels until 63 hours after entry.

CASE 4K.—P. S., a 6½-year-old white female, was admitted to St. Louis Children's Hospital because of progressive weight loss (14 pounds), polyuria, and polydipsia of two months' duration. Five days prior to entry vomiting, abdominal pain and weakness developed, and seventy-two hours later the child was drowsy and refused food.

Physical examination revealed a malnourished, dehydrated, acutely ill child, who was semicomatose. The respirations were deep and pauseless. The pharynx was diffusely injected. Blood chemical studies revealed a serum HCO_3 of 9.5 meq. per liter, serum K of 5.8 meq. per liter and a serum true glucose of 520 mg. per 100 ml. (Table II). The urine sugar was 4 plus, and the $FeCl_3$ test was strongly positive. The electrocardiogram revealed RS-T segment depression in L_2, aV_R, aV_F, V_3, V_4, V_5, and V_6, and flattening of the T waves in L_1, V_3, V_4, V_5, and V_6 (Fig. 4). Thirty milliliters per kilogram of 1/6 molar sodium lactate was given by intravenous drip and 15 ml. per kilogram of 1/6 molar sodium lactate and 20 ml. per kilogram of KCl solution containing 2 Gm. of KCl (1.67 meq. per kilogram) were given subcutaneously. In seven hours the patient was markedly improved and the serum HCO_3 was 17.6 meq. per liter. At this time the electrocardiogram revealed an accentuation of the depression of the RS-T segments and flattening of the T waves. Fourteen hours after the start of therapy the child was alert and ate breakfast. The blood chemistries were normal except for a serum Na of 133.5 meq. per liter and serum K of 3.3 meq. per liter. The T waves were flattened, but the RS-T segments showed only slight deviation. By 63 hours the electrocardiogram was within normal limits and the remainder of the hospital stay was uneventful.

CASE 5K.—K. L. W., a 6-year-old white male, was a known diabetic of one and one-half years' duration controlled with NPH insulin given each morning. Forty-eight hours prior to admittance the child complained of feeling poorly, and shortly afterward started vomiting which continued up to entry. On the morning of hospitalization the patient received 34 units of NPH insulin subcutaneously.

The initial physical examination revealed an acutely ill, semicomatose child who was markedly dehydrated. The skin turgor was poor and skin lesions, typical of granuloma annulare, were present on the ankles, legs, and left wrist. The remainder of the physical examination was negative except for deep, pauseless respirations.

The initial laboratory studies revealed a serum HCO_3 of 12.7 meq. per liter, and a serum true glucose of 450 mg. per 100 ml. (Table II). One unit per kilogram of regular insulin was given subcutaneously followed by 20 ml. per kilogram of lactate Ringer's. Thirty milliliters per kilogram of Ringer's plus 30 ml. per kilogram of distilled water with 3.4 Gm. (1.9 meq. per kilogram) of KCl was added. The serum HCO_3 was 21.9 meq. per liter by 20 hours and the serum K never dropped below 4.1 meq. per liter. The electrocardiograms failed to reveal any abnormalities at any time (Fig. 4).

CASE 6K.—R. W., a 5-year-old Negro female, entered the hospital with a

history of weight loss, polydipsia, polyuria, polyphagia, and lethargy developing over a period of three weeks. Examination revealed a severely dehydrated, malnourished child in a semicomatose state. The respirations were Kussmaul in type. The tympanic membranes were injected and the tonsils were moderately hypertrophied. Laboratory examination revealed a serum HCO_3 of 8.5 meq. per liter, serum K of 5.1 meq. per liter, and serum true glucose of 405 mg. per 100 ml. (Table II). The electrocardiogram at this time was within normal limits (Fig. 4). Six hundred milliliters of 1/6 molar sodium lactate (40 ml. per kilogram) was started by intravenous drip in the emergency room and later a subcutaneous infusion of 450 ml. of 1/6 molar sodium lactate (30 ml. per kilogram) and 600 ml. of KCl solution containing 3.4 Gm. (3.0 meq. per kilogram) of KCl was started upon arrival on the ward. Eight hours after the initiation of therapy the serum HCO_3 was 22 meq. per liter and the serum potassium was 4.3 meq. per liter. The electrocardiogram revealed flattened or inverted T waves and depression of the RS-T segments in V_5 and V_6. The next morning, eighteen hours after entry, the patient was alert and ate breakfast. The serum HCO_3 was 30.3 meq. per liter, serum Ca 8.8 mg. per 100 ml., and serum K 3.1 meq. per liter. The T waves were broad and flat. By 66 hours the electrocardiogram was normal and the serum K 3.8 meq. per liter.

CASE 7K.—V. L. C., a 3-year-old white female, was admitted to the hospital with a history of polyuria, polydipsia, weight loss, and easy fatigability of four weeks' duration. Five days prior to entry she became listless and twenty-four hours before admittance she was noted to be hyperventilating. On the day of hospitalization the parents noted a "fruity" odor to her breath.

Physical examination revealed an acutely ill, malnourished child who was semicomatose. The eyes were sunken and soft, and the skin dry with poor turgor. The remainder of the physical examination was negative except for a moderately injected pharynx. Laboratory examination revealed a HCO_3 of 8.9 meq. per liter and a serum true glucose of 417 mg. per 100 ml. (Table II). The initial electrocardiogram showed flattening of the T waves in all leads (Fig. 4). Two units per kilogram of regular insulin were given subcutaneously and 460 ml. (38 ml. per kilogram) of 1/6 molar sodium lactate intravenously. Four hundred fifty milliliters of 1/6 molar sodium lactate with 600 ml. of sterile distilled water plus 3 Gm. (3.4 meq. per kilogram) of KCL were given subcutaneously over the next fourteen hours. Seven hours after the initiation of therapy the HCO_3 was 25 meq. per liter and the serum K was 3.4 meq. per liter. The electrocardiogram at this time was essentially unchanged and the child was alert and taking oral feeding. Twenty-four hours after entry the blood chemical values were essentially normal and the child was alert, but the electrocardiogram did not return to normal until 44 hours later.

DISCUSSION

There are many reports which have emphasized the role of potassium in metabolic acidosis and recommended the administration of potassium orally or parenterally after the initial hydration. The use of parenteral potassium, however, has not been required in any diabetics in acidosis who were treated according to the Hartmann regime, nor has it been necessary to add oral potassium to the diet. The rapid recovery in these patients enables them to take a normal diet which contains from 3 to 5 meq. per kilogram per twenty-four hours in addition to adequate amounts of protein, carbohydrate, and fat.

The difficulties involved in trying to compare treatment regimes, with and without parenteral potassium in

the initial treatment in such a complex disturbed metabolic state as diabetic acidosis, are obvious. The number of cases in the two groups reported is small, but it will be possible to demonstrate that there is little difference between the clinical and blood electrolyte responses in the two groups.

The case summaries include fifteen patients with diabetic acidosis who were treated according to the Hartmann regime and seven patients treated in the same manner except that added parenteral potassium was included in the initial therapy. The total water and electrolyte therapy is summarized in Table III. One can see that the essential difference between the two groups is the quantity of K given. The K-treated patient also received slightly less Na and Cl.

The majority of the cases included in both groups were either in extreme or severe metabolic acidosis and the classification of the patients according to Hartmann[5]* would be as follows:

Group I (Cases Without Added K)

Extreme acidosis—2a, 2b, 7, 9, 12
Severe acidosis—1, 3, 4, 6, 10, 11, 13, 14, 15
Moderate—5, 8

Group II (Cases With Added K)

Extreme acidosis—2K, 3K
Severe acidosis—1K, 4K. 5K, 7K
Moderate—6K

It was difficult to quantitate the clinical response of the patients in the two groups. An attempt was made to compare the response of the groups and no difference could be found as to:

1. Disappearance of ketosis.
2. Correction of hyperglycemia.
3. Clinical recovery as judged by disappearance of lethargy, ability to take food, and amount of activity.

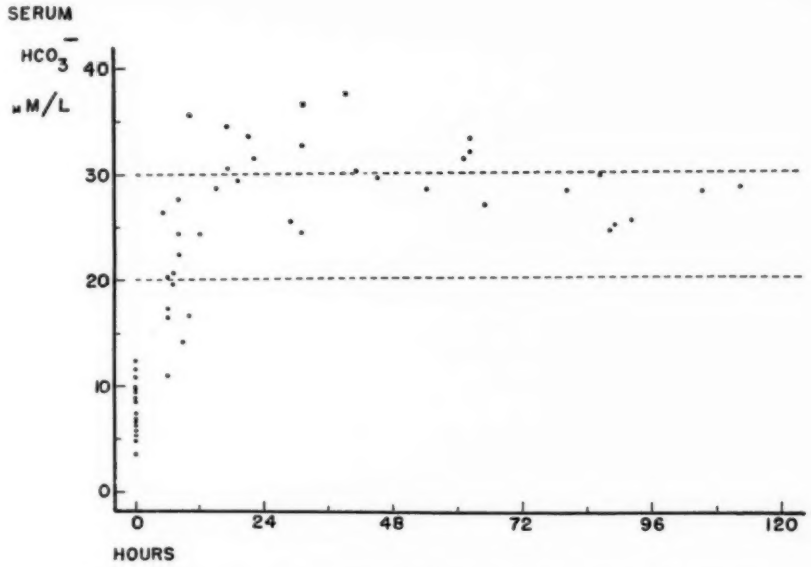
All the children were alert and eating between eight and fourteen hours after entry. Ketosis, as judged by the $FeCl_3$ test of the urine, disappeared in all cases by 19 hours. The rate of recovery from acidosis was analyzed in Graphs I and II. In all cases the HCO_3 was above 20 meq. per liter by 18 hours and there was no difference in rapidity of disappearance of acidosis.

As can be seen in Graph I, six cases in Group I showed slight overriding above the 30 meq. per liter HCO_3, but no clinical manifestations of alkalosis could be detected. We do not feel that this minimal degree of alkalosis is in any way detrimental to the recovery of children from diabetic acidosis.

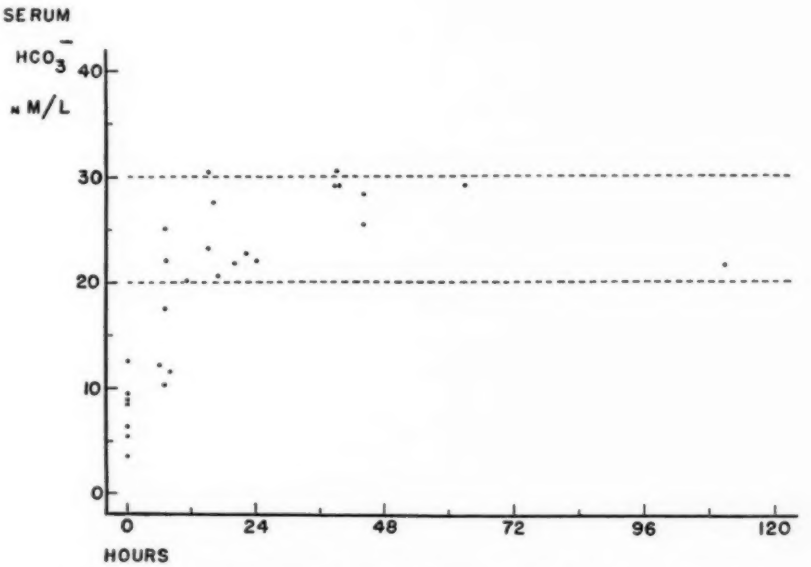
TABLE III. SUMMARY OF FLUID AND ELECTROLYTE THERAPY OF PATIENTS WITH ADDED POTASSIUM

NAME	H_2O ML./KG.	NA MEQ./KG.	K MEQ./KG.	CL MEQ./KG.	LACTATE MM./KG.
1K. V. J. S.	98.0	13.2	0.81	4.3	9.9
2K. P. A. W.	100.0	9.1	5.2	4.5	10.0
3K. L. K. H.	112.0	11.6	2.2	3.1	10.8
4K. P. S.	90.7	10.8	1.7	4.1	7.9
5K. R. W.	108.0	11.5	3.0	3.0	11.5
6K. K. L. W.	111.0	12.3	2.1	5.3	9.3
7K. V. L. C.	127.0	13.0	3.4	3.4	13.0
Theoretical	100.0	14.0	0.2	4.5	10.0
30 ml. 1/6 M Na lactate					
30 ml. 1/6 M Na lactate					
40 ml. R.S.C.					

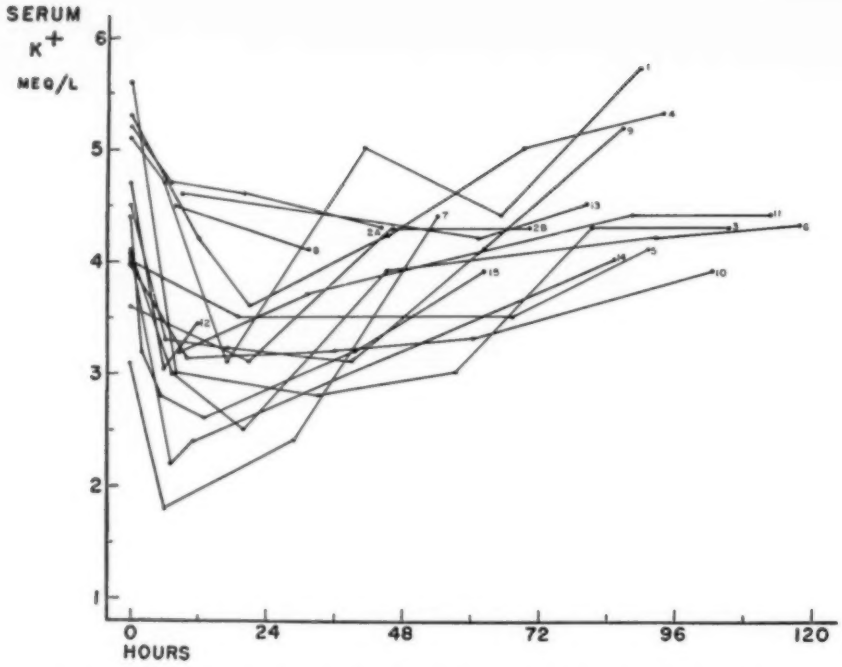
*Hartmann Classification of Metabolic Acidosis:
Extreme, 2.5—6.3 meq./L HCO_3.
Severe, 6.4—10.6 meq./L HCO_3.
Moderate, 10.7—14.8 meq./L HCO_3.
Mild, 10.9—19.1 meq./L HCO_3.



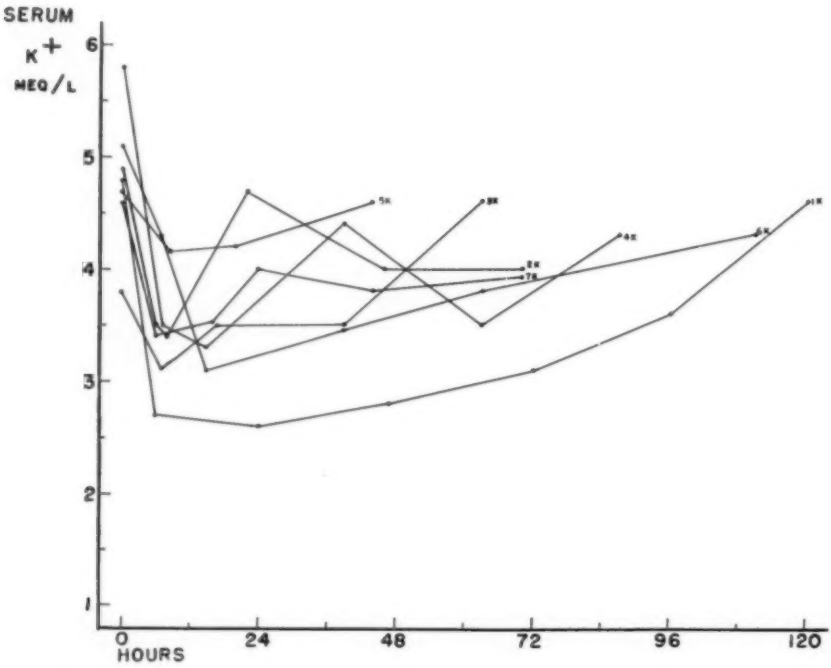
Graph I.—Serum bicarbonate levels of patients treated without added potassium.



Graph II.—Serum bicarbonate levels of patients treated with added potassium.



Graph III.—Serum potassium levels of patients treated without added potassium.



Graph IV.—Serum potassium levels of patients treated with added potassium.

The HCO_3 response of the K-treated children is shown in Graph II, and one patient exceeded the normal HCO_3 range.

The two groups were also analyzed in Graphs III and IV, as to the serum K levels during their recovery phase. Both groups showed an initial drop in serum potassium which frequently went below 3.5 meq. per liter, but only two cases in the group which did not receive added potassium showed a drop below 2.5 meq. per liter. It should be re-emphasized that no case showed any evidence of hypokaliemia such as weakness or paralysis of any muscle groups, abdominal distention, nausea, vomiting, cardiac enlargement, or evidence of cardiac failure. It might also be added that Hartmann, in his series of over 200 cases of diabetic acidosis, has not encountered the above picture.

Evidence of hypokaliemia was looked for in serial electrocardiograms which were obtained during the course of therapy. These tracings were studied for evidence of correlation between serum potassium levels and electrocardiographic abnormalities. No definite correlation could be demonstrated. This has been noted in previous publications.[9, 10]

The ability to demonstrate hypokaliemia in man, electrocardiographically, is very questionable. The electrocardiographic changes seen in these patients are not unusual and have been reported by other investigators. It seems doubtful, however, that these transient changes observed could be explained upon the single ion effect of potassium in such a complex disturbed metabolic state as diabetic acidosis.

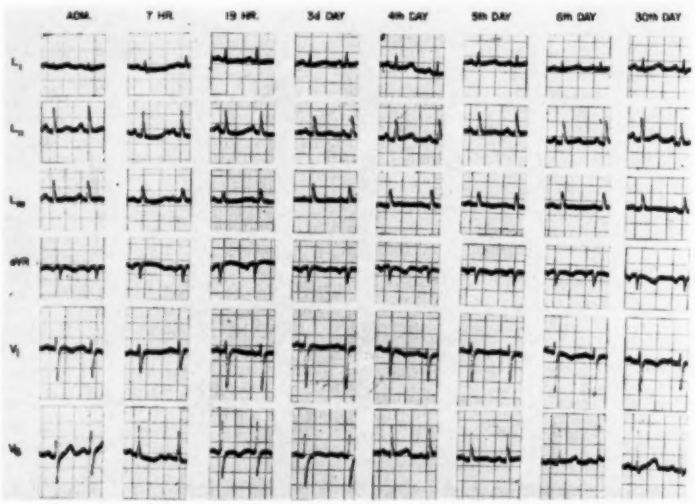


Fig. 5.—Serial electrocardiograms on patient D. J. K. (No. 6).

It may be pointed out that eight out of fifteen patients in the group without added K showed depression of the RS-T segment and four out of seven patients in the K-treated group demonstrated similar changes. This depression of the RS-T segment showed

better correlation with the serum HCO_3 level than with the serum K. The changes in the RS-T segment disappeared in twelve to eighteen hours in both groups.

The T-wave changes (flattening or increase in width) were usually observed after the first 24 hours, and the degree and duration of flattening did not parallel the serum potassium level in the cases considered individually. It is of interest to point out that patient D. J. K. showed flat and broad T waves at 90 and 114 hours after admittance which were similar to those seen during the initial 48 hours, even though the tracing at 67 hours was within normal limits and the patient was ambulatory and eating a full diabetic diet (Fig. 5). Similar findings were observed in other cases.

SUMMARY

1. The blood chemical determinations and serial electrocardiograms of fifteen juvenile diabetics in moderate to extreme acidosis are reported.

2. These patients were treated according to the Hartmann regime and did not receive added K initially in any instance. The clinical syndrome of hypokaliemia was not observed.

3. No parenteral potassium therapy was necessary since all patients responded rapidly and were taking either liquid or soft diets in the first 24 hours and were ambulatory in 48 hours.

4. A group of seven juvenile diabetics in severe or extreme acidosis received added parenteral K initially and were studied in a similar manner.

5. The serum potassium levels were followed and showed the usual early depressions as in Group I but there seemed to be no correlation with the clinical state of the patient or the serial electrocardiographic findings.

6. No significant differences could be seen in the electrocardiograms of Group I and Group II.

7. There seems to be a reasonable doubt that the electrocardiographic changes can be attributed solely to hypokaliemia but may be the result of other factors in such a disturbed metabolic state as diabetic acidosis.

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CONVULSIONS IN TUBEROUS SCLEROSIS CONTROLLED BY ELIMINATION OF IMPULSES ORIGINATING IN THE BASAL GANGLIA

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THE subcortical origin of major convulsive seizures has only rarely been established with certainty. Clinical seizures may start before significant changes develop in the scalp electroencephalogram. For example, Lennox and Brody[4] noted in a patient thought to have a thalamic tumor that clinical attacks began one and one-half minutes before the development of abnormalities in the scalp EEG. Penfield and Jasper[8] described in their monograph the case of a girl in whom an aura of pain in the knee joint and sensation of cold with shivering occurred without significant changes in the EEG. When the attack progressed to the stage of myoclonic jerks, multiple spike and wave complexes appeared bilaterally from the frontocentral regions. These authors assumed that in this case the attack started in the higher brain stem (hypothalamus) and continued for several seconds until it reached a subcortical motor system which gave rise to bilateral myoclonic jerks and evoked potentials of the primary synchronous type.

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In the following case, the subcortical origin of generalized convulsions, as well as of minor seizures, is made highly probable by the cessation of seizures following elimination of a subcortical focus.

CASE REPORT

W. S., a 10-year-old white boy, had a history of convulsions of increasing severity which were refractory to anticonvulsant medication and were associated with progressive mental deterioration. His early history revealed that he was born at home following an uneventful pregnancy and a spontaneous delivery. A severe tonic and clonic convulsion occurred on the third day of life. His early life was marked by repeated convulsions and mental retardation. He did not sit alone until 18 months of age, walk without support until 2½ years, or run until 4 years.

At the time of his first visit to St. Christopher's Hospital for Children, at 5 years of age, he was physically well developed. There were no focal neurological signs. He ran semipurposefully about the examining room. Occasionally he stopped for no apparent reason and rocked back and forth while overbreathing. He then developed a series of minor seizures, characterized by nodding of the head, extension of the arms, and flexion at the waist. If he happened to be erect, he fell forward. The presence of a butterfly distribution of adenoma se-

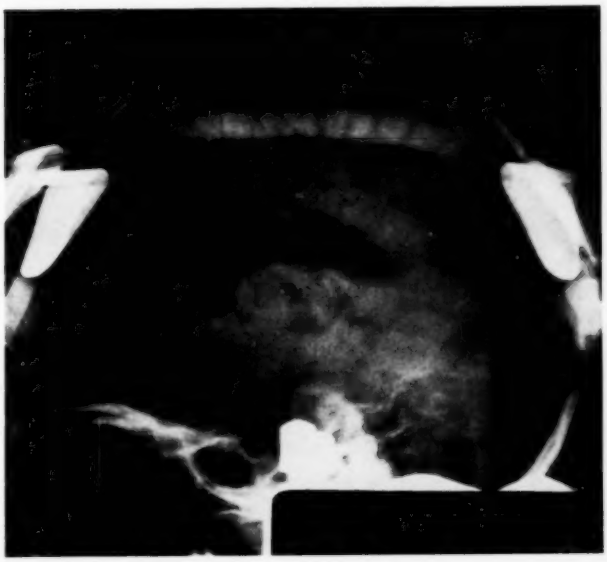
baccum over the nose and cheeks, an intracranial calcification demonstrated roentgenographically, and tubercles in the fundi suggested the diagnosis of tuberous sclerosis.

The ophthalmologic changes have been described in detail by Pagenstecher.[7] The significant findings in this boy were noted in the fundus of the left eye where four small tumor masses were present. The largest was 1 by 2 disc-diameters in size, gray white, and rose 2 to 3 diopters above the level of the surrounding retina. Three of these mulberry-like lesions were closely associated with the temporal vessels.

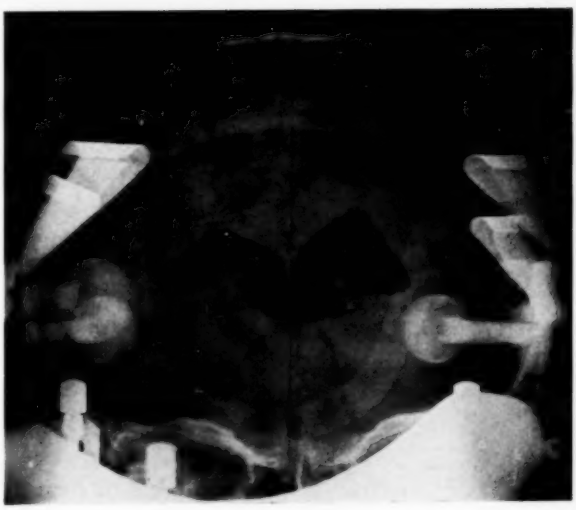
During the next five years, various anticonvulsant drugs were used alone and in combination in an unsuccessful attempt to control his major and minor convulsive episodes; included was the Putnam regimen of narcosis produced by Dilantin. By the time of his admission in January, 1955, mental deterioration was marked. He could no longer sit by himself, walk even with support, recognize his name, or feed himself. He was reported to have 250 or more series of minor convulsions a day and two or three generalized tonic and clonic convulsions each week. Large doses of phenobarbital, Dilantin, Mebaral, Mysoline, and Tridione were used alone and in combination, e.g. (1) phenobarbital up to 180 mg. daily and Dilantin up to 400 mg. daily, (2) phenobarbital up to 180 mg. daily, Dilantin up to 400 mg. daily, and Tridione up to 2,700 mg., etc. In addition there were observation periods during which no anticonvulsant medication was given. In order to control the seizures such high doses of anticonvulsant drugs were needed that they narcotized the patient.

Fig. 1.—Intracranial calcification.

Since the roentgenographic studies revealed only a single subcortical calcified nodule (Fig. 1) that seemed to lie, according to the air studies (Fig. 2), in the region of the right caudate nucleus, it was felt that the seizure discharges might originate in the



A.



B.

Fig. 2.—Calcification (arrow) in relation to lateral ventricle. *A*, Lateral view; *B*, antero-posterior view.

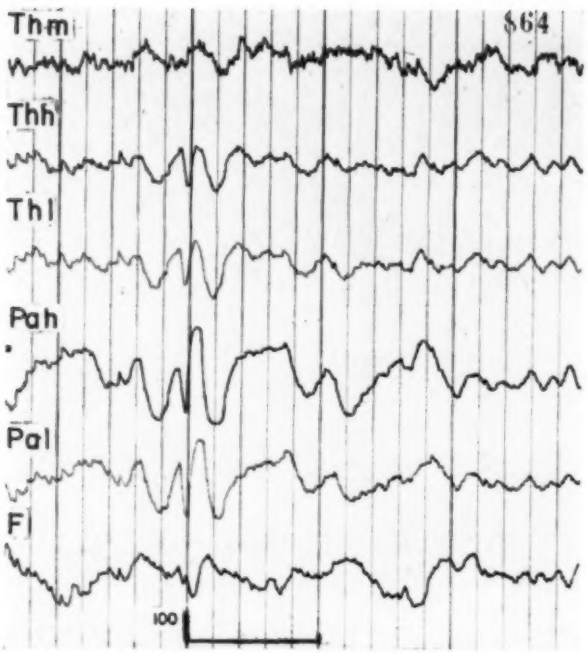
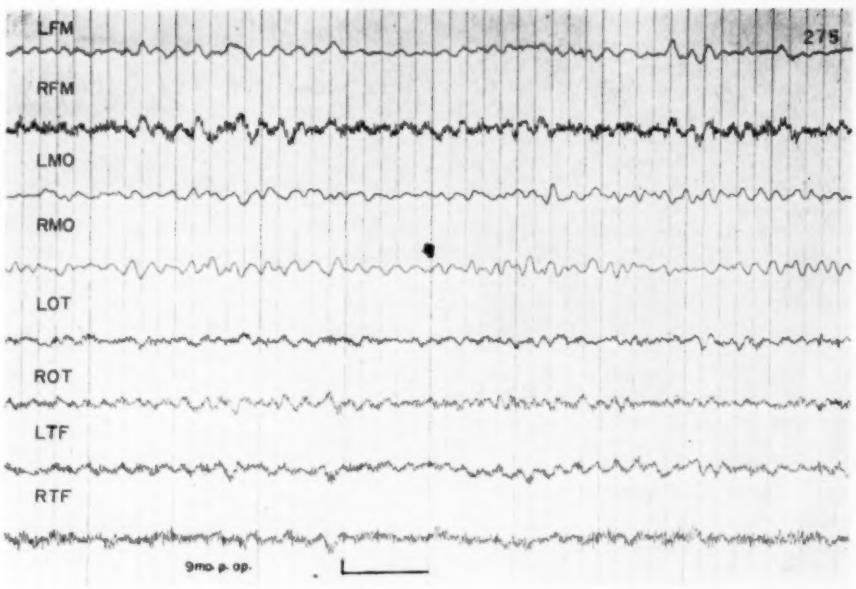


Fig. 3.—Monopolar depth electroencephalogram from the right thalamus (*Th*: *m*, middle; *h*, upper; *l*, lower electrode), and from the right pallidum (*Pa*: *h*, upper; *l*, lower electrode); *F*, frontal scalp lead. Time: one second. Standardization in microvolts.

Fig. 4.—Preoperative scalp EEG. Patient spontaneously asleep. *LFM* (*RFM*) left (right) frontomotor leads; *LMO* (*RMO*) left (right) motor-occipital leads; *LOT* (*ROT*) left (right) occipitotemporal leads.



A.

B.

Fig. 5.—Scalp EEG nine months after operation. *A*, Patient falling asleep. *B*, Patient asleep. *LTF* (*RTF*) left (right) temporofrontal leads. Other abbreviations, standardizations, and time marked as in Fig. 4.

basal ganglia, and recording electrodes were inserted in the globus pallidus and in the thalamus (dorsomedial nucleus and centrum medianum). Records from these nuclei and the scalp showed spike discharges mostly appearing simultaneously in these three areas so far as could be judged from the records taken with the Grass EEG apparatus. Cathode ray oscillograms that may have revealed small time intervals between the pallidal and the other discharges were not taken. On monopolar records the spikes were negative in the pallidum and positive in the scalp. In several places the amplitudes of the discharges from the pallidum were definitely larger than those from the scalp or from the thalamus (Fig. 3). This suggested a focus in or near the pallidum.

On Feb. 10, 1955, electrolytic anodal lesions in the area of the calcification and in the right ansa lenticularis were produced using a needle electrode that was inserted by means of the stereoencephalotome. The postoperative course was uneventful. No further major or minor seizures occurred. He was discharged on phenobarbital, 60 mg. twice daily, and Dilantin, 150 mg. twice daily, on Feb. 25, 1955.

By March 3, 1955, he had begun to crawl and to feed himself. No convulsions occurred. He seemed aware of his surroundings and recognized his mother.

On March 30, 1955, he had begun to walk with support. During the next three months his general improvement continued. He began to follow simple commands, run, and express simple wants.

This child has done well at home. There have been no further convulsions during the postoperative observation period of fifteen months. The medication was gradually reduced and he receives, rather irregularly, phenobarbital, 30 mg. daily, and Dilantin, 30 mg. daily.

It seems of interest to compare the preoperative and postoperative scalp electroencephalograms (Figs. 4 and 5).

The preoperative EEG examination, taken without additional sedation, revealed rather irregular low voltage delta waves (Fig. 4). Against this background repeated spike discharges appeared in various leads, particularly in the frontal and central leads. Nine months following the operative procedure, the EEG, which was again taken without additional sedation, showed a much more regular 4 to 6 per second rhythm when the patient started to fall asleep (Fig. 5, *A*); when the patient was asleep, only occasionally spike discharges were noticeable, chiefly in the frontal leads (Fig. 5, *B*).

DISCUSSION

These observations seem to be of interest for two reasons: (1) They show that subcortical electroencephalography is not only of theoretical interest but may also, in conjunction with other methods such as roentgenographic studies, help to localize a subcortical epileptogenic focus that may be amenable to surgical treatment. (2) They seem to suggest with a rather high degree of probability that seizures may originate in the striopallidum. In this patient the seizures did not reappear for the duration of the postoperative observation (over fifteen months) after elimination of the nodule in the caudate nucleus and interruption of the centrifugal fibers from the striopallidum in the ansa lenticularis. During this time the medication was drastically reduced, e.g., phenobarbital to one-sixth, Dilantin to one-thirteenth of the preoperative daily doses. The possibility that another focus may exist that so far could not be definitely localized cannot be completely excluded, since the EEG, although markedly improved, still showed occasional spike discharges in the frontal leads. However, such an addi-

tional focus, if present, has not been sufficient to produce clinical seizures. In view of the possibility of such an additional focus, we have hesitated to discontinue anticonvulsive medication completely. The improvement in the behavior of the patient, e.g., in his ability to react to his environment, and the improvement in the EEG record may be due partly to the marked reduction in the medication, and partly to recovery of the cells of the central nervous system from the secondary effects of repeated convulsions.

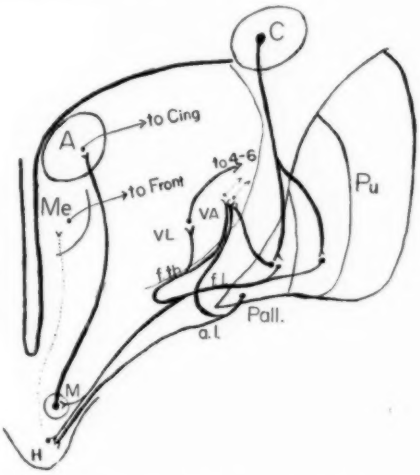


Fig. 6.—Strio-pallido-thalamo-cortical circuits. *A*, Anterior nucleus; *a. l.*, ansa lenticularis; *C*, caudate nucleus; *Cing*, gyrus cinguli; *Front*, frontal cortex; *H*, hypothalamus; *f.l.*, fasciculus lenticularis; *f.th.*, fasciculus thalamicus; *M*, mammillary body; *Me*, nucleus medialis (dorsomedial nucleus); *Pall*, pallidum; *Pu*, putamen; *VA*, nucleus ventralis anterior; *VL*, nucleus ventralis lateralis.

A brief discussion of the possible pathways by means of which a focus located in the striatum may cause generalized epileptiform convulsions may be in order (Fig. 6). The impulses from the striatum pass first into the pallidum as demonstrated by the classical experiments of Wilson.[13] Pallidofugal impulses may, on the one hand, reach the subcortical centers of the extrapyramidal system; on the other hand, they may reach the dorsal thalamus in part directly, and in part by way of the hypothalamus. Fibers of the fasciculus lenticularis form a loop in Forel's field and ascend in the fasciculus thalamicus to the nucleus ventralis anterior[9] and to the nucleus ventralis lateralis.[2] The nucleus ventralis anterior receives also pallidal impulses directly and through the ansa lenticularis. Pallidohypothalamic fibers in part go to the ventromedial nucleus of the hypothalamus, in part to the mammillary body.[2]

From the nucleus ventralis lateralis of the thalamus impulses reach the motor and premotor areas. The nucleus ventralis anterior may also participate in the transmission of pallidal impulses to these regions.[6] Jasper and associates,[3] however, regard it as part of the nonspecific thalamocortical projection system. From the

hypothalamus, periventricular fibers reach the dorsomedial nucleus that projects to the frontal lobe, and from the mamillary body the Vicq d'Azyr bundle ascends to the anterior nucleus which sends axons to the gyrus cinguli.

It is known from animal experiment that stimulation of the caudate nucleus may alter the electrical discharges of the cerebral cortex.[1, 10, 12] Observations of Spiegel and associates[11] in patients in whom they stimulated the ansa lenticularis and ventral part of the pallidum preceding pallidoansotomy have shown that also in man impulses from the pallidum reach the cerebral cortex. In their studies stimulation of the ansa produced evoked potentials in the EEG that probably reflected cortical reactions.

An interruption of these strio-pallido-diencephalo-cortical circuits can be accomplished relatively easily by stereotactically produced pallidoansotomy. In a properly selected patient such a procedure is able to produce cessation of the seizures originating in the basal ganglia as is demonstrated in the boy under study.

SUMMARY

Control of major and minor seizures in a 10-year-old boy with tuberous sclerosis is reported. In conjunction with roentgenographic studies a striatal focus was located by depth electroencephalography, and circumscribed lesions were produced in this area and the corresponding ansa lenticularis. The recording as well as the coagulating electrodes were inserted by means of the stereoencephalotome. The practical and theoretical implications of these observations are discussed.

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INTRAMUSCULAR IRON FOR THE TREATMENT OF IRON DEFICIENCY ANEMIA IN INFANCY

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SAN FRANCISCO, CALIF.

IRON deficiency is a common cause of anemia in infants between 6 months and 2 years of age.[1, 2] Severe iron deficit once incurred cannot be repaired by improved diet alone and medicinal iron must be given. Oral iron adequately corrects the hemoglobin deficiency, but, unless continued for many months, does not replenish iron storage.[3] Since many anemic children are already poor eaters, it is especially difficult to give them potent iron preparations, which are relatively unpalatable. The problem is further complicated because food, especially milk, must not be given with iron, since insoluble precipitates may be formed rendering iron unabsorbable. Parenteral iron has the advantage of easy administration and better production of iron storage. Colloidal suspensions of saccharated iron oxide have been available for intravenous use since 1947 and are quite effective.[4-8] Technical difficulties with intravenous administration to small infants, occasional venospasms, and minor reactions, such as fever and drowsiness, have been drawbacks. A recently introduced iron dextran complex for intramuscular use was designed to eliminate some of these difficulties.[9-11]

From the Research Laboratory, Children's Hospital.

The expenses of this investigation were defrayed in part by a grant from General Foods Corporation.

MATERIAL AND METHODS

All children were seen on the wards or in the outpatient department of Children's Hospital. Their ages ranged from 2 to 26 months. Detailed hematologic data are given on four infants. Intramuscular iron was given to another ten children with iron deficiency anemia. The diagnosis of iron deficiency anemia was established by the characteristic blood picture, lack of bone marrow hemosiderin, and an eventual return to normal values following iron therapy. Red cell counts were done using two pipettes and one chamber. Hemoglobin determinations were made by the oxyhemoglobin method using a Beckman model B spectrophotometer. Reticulocytes were enumerated daily using the dry method and counting 1,000 cells. Bone marrow hemosiderin determinations were made using the Prussian blue reaction.[12] Imferon* was given in 1 to 2 ml. doses, representing 50 to 100 mg. elemental iron. Total dosage was given according to age: under 12 months, 200 mg.; 12 to 24 months, 300 mg.; over 24 months, 400 mg. Dosage was based on average iron content in newborn infants[13] and average annual iron increments in childhood.[14] Injections were given daily and made into the gluteus

*Kindly supplied by Benger Laboratories, Ltd., Holmes Chapel, Cheshire, England.

muscle. The patients were carefully watched for fever, nausea, vomiting or diarrhea, and local inflammatory reactions.

RESULTS

Morphologic data are given in Table I. It is evident that prompt hemoglobin responses were made in all four patients and that levels of about 12 grams were reached in three weeks regardless of pretreatment values. In the two severely anemic patients the initial rate of hemoglobin production exceeded 3 per cent per day. Red cell counts showed transient rises to values above normal. Spectacular reticuloeyte rises were occasionally seen; in one patient the

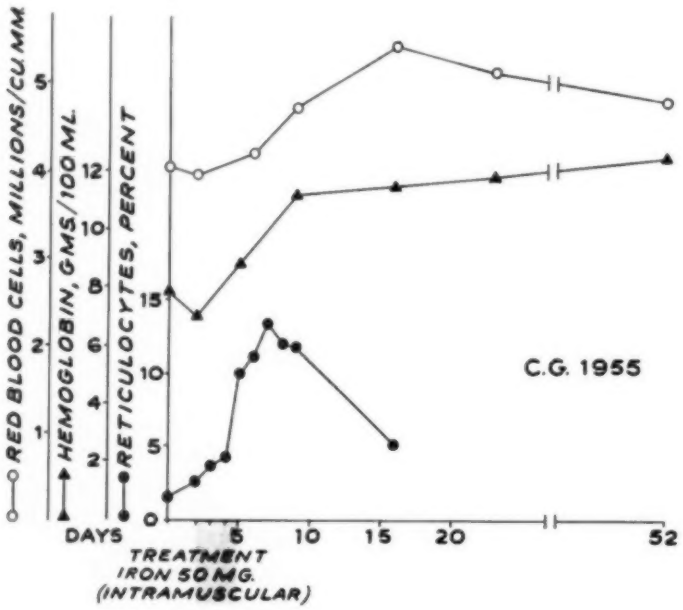

Fig. 1.

TABLE I. RESPONSE OF IRON-DEFICIENT INFANTS TO INTRAMUSCULAR IRON

DAYS AFTER INITIAL Rx	C. G., 6 MO.			T. B., 18 MO.			R. H., 24 MO.			P. S., 26 MO.		
	RBC	Hg	RETICS.	RBC	Hg	RETICS.	RBC	Hg	RETICS.	RBC	Hg	RETICS.
0	3.9	6.9	2.5	5.6	8.7	1.8	4.6	8.7	2.3	2.4	3.0	2.3
1			3.4			2.2			2.5			3.2
2			4.1	5.9	9.3	2.5			1.9			5.1
3			10.0						1.9	2.3	2.7	6.9
4	4.4	8.7	11.1			3.0	6.1	10.0	1.7			9.1
5			13.4	6.2	9.3	4.9			1.2			15.2
6			12.0			5.1				2.8	5.4	12.5
7	4.7	11.1	11.9	6.2	11.1	3.9	5.4	10.5	0.8			13.0
2 wk.	5.4	11.4	5.0	5.7	11.4		5.3	10.8		3.5	9.3	12.2
3 wk.	5.1	11.7		6.1	12.3		5.6	12.0		4.6	11.1	2.4
7 wk.	4.8	12.3		5.5	12.0		4.6	12.6		5.1	13.2	

Note.—RBC: $\times 10^6$/mm.^{3} Hg: Gm./100 ml. Retics.: per cent.

peak was 13.4 per cent, equivalent to 600,000 cells by absolute count. However, reticulocyte responses were not uniform and one patient made none at all. Reticulocytes began to rise quite early; there frequently was a suggestion at twenty-four hours and a definite response in forty-eight hours. Peak values occurred about the fifth day.

In the bone marrow, hemosiderin, which was absent in all cases before therapy, could be demonstrated by the Prussian blue reaction twelve hours after intramuscular injection. The injections caused no local pain, tenderness, redness or swelling, but slight brownish discoloration of the subcutaneous tissues was seen in one infant and lasted for a week. There were no systemic reactions such as fever, lethargy, nausea, or diarrhea in any of the patients.

DISCUSSION

Iron balance in infancy is precarious,[15, 16] and iron must be absorbed after the first four months of life to increase hemoglobin mass along with body mass. Inadequate diet, poor utilization, or blood loss may lead to deficiency and anemia. When anemia develops, the best treatment is iron rather than blood. Iron repairs the mineral deficiency more specifically, and since its parenteral forms are dispensed in more concentrated solutions than blood, there is no problem of overloading the circulation (iron content of iron dextran, 50 mg. per milliliter; saccharated iron oxide, 20 mg. per milliliter; red cells, 1 mg. per milliliter; whole blood, 0.5 mg. per milliliter). Untoward reactions are probably less frequent with parenteral iron, especially when given intramuscularly.

In adults indications for parenteral iron are, as a rule, restricted to oral intolerance, obvious intestinal disorders, and uncontrollable chronic bleeding. In children the same indications are valid but a more frequent indication, perhaps, has to do with practical patient management. In pediatric outpatient practice regular attendance and faithful drug taking are frequent problems. Oral iron is often not taken long enough to repair the deficiency completely, and safe parenteral iron medication involving only one to four injections has a great practical advantage.

In this study hematologic changes were entirely comparable to those seen after intravenous iron and slightly faster than those following oral iron. The prompt reticulocyte responses and appearance of hemosiderin in the marrow indicated good absorption from the injection site. Return to normal red cell indices in three months showed that enough iron was given. Clinically a return of appetite and feeling of well-being paralleled reticulocyte and hemoglobin rises.

One hesitation about the use of parenteral iron has been the fear of producing hemosiderosis or even hemochromatosis. Since there is no mechanism for iron excretion, other than bleeding, iron injected means iron retained, and excessive therapy may lead to iron overload. However, there is a wide margin of safety, and at least 2 or 3 Gm. may be given to infants with impunity. It must be strongly emphasized that failure to respond to the proper dose of intramuscular iron is never an indication

for giving more iron. There are two possible reasons why hypochromic, microcytic anemia might not improve after iron; either the diagnosis of iron deficiency anemia was wrong, the patient has a congenital red cell abnormality such as thalassemia minor,[17] or his bone marrow is inhibited by an intercurrent infection such as pneumonia or nephritis. In either case additional iron must not be given.

CONCLUSIONS

1. Imferon given intramuscularly effected hemoglobin rises of 1 to 4 per cent per day in four infants with iron deficiency anemia.

2. Reticulocyte rises were not uniformly obtained.

3. There were no untoward local or systemic reactions.

4. Imferon given intramuscularly appears to be a safe, effective, and convenient form of iron treatment in infancy.

I am indebted to Mrs. Aline Napp for the performance of the blood examinations.

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PORTAL HYPERTENSION IN A CHILD DIAGNOSED BY SPLENOPORTOGRAM

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CASE REPORT

ON Oct. 21, 1954, a 2½-year-old white female child was admitted to the Albert Einstein Medical Center, Northern Division, for the third time. The chief complaint on this admission was hematemesis which had started on the day prior to admission and was associated with the passage of tarry stools. The mother reported that for several months the child had episodes of epistaxis.

According to the family history, there had been no bleeding tendencies, except for an older brother who had epistaxis about a year before. There were no abnormalities noted on recent examination of the older brother.

The child was born at the Albert Einstein Medical Center, the seventh child of a 40-year-old, Rh-negative mother. All other siblings are living and well. During this pregnancy, glucose tolerance tests and electrocardiograms were done on the mother because all previous children had weighed over 11 pounds at birth. All of these tests proved normal.

The child weighed 11 pounds 2 ounces at birth, and was Rh positive. Coombs test was negative; red blood count was 5,049,000; hemoglobin was 19.7; and there were no nucleated red blood cells. There was no sign of hemolytic disease. The baby was kept in the hospital at that time because of fever, regurgitation, and a foul-odored cord stump. Recovery was uneventful. Five days after she was discharged, she was readmitted because of a rash which was diagnosed as erythema multiforme. At this time she remained in the hospital for five days.

Physical examination on the third admission revealed a well-developed, well-nourished child whose skin was warm, dry, and pale. Ears, nose, and throat were normal. The heart rhythm was regular, and the chest was clear. The abdomen was soft, the liver not palpable, and the spleen just palpable under the left costal margin. There was no venous distention noted, nor visible collateral veins of the abdomen and no lymphadenopathy present. Temperature was 100° F., respiration 24, and pulse 100. Hematemesis continued three times a day, three or four tarry stools were passed, and there was an attendant anemia (see Fig. 1).

During her life she had taken little in the way of solid food, no vitamins, but subsisted principally on milk. Because of the severe anemia, a blood transfusion was given. After this, the spleen extended three fingerbreadths below the costal margin (Fig. 2). The stools gradually became normal in color, but the occult blood reports remained positive.

Complete gastrointestinal and x-ray studies revealed esophageal varices (Fig. 3). There were no other significant findings. Bone marrow study showed general hyperplasia. Urinalysis, blood chemistry, serology, and electrocardiographic findings were within normal limits. The purified protein derivative was negative. Though liver function tests were normal, the splenomegaly and the pres-

These studies were made at the Albert Einstein Medical Center, Northern Division, Philadelphia, under the service of Robert A. Schless, M.D., and the X-ray Department.

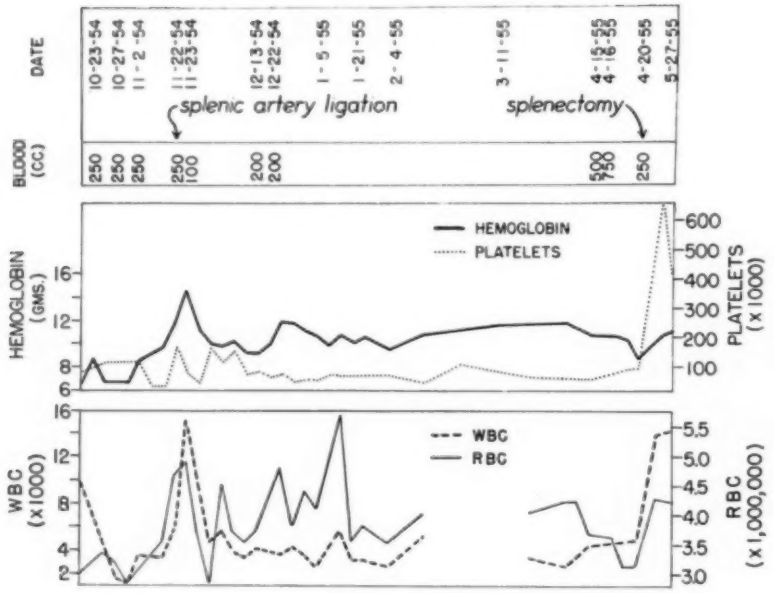

Fig. 1.

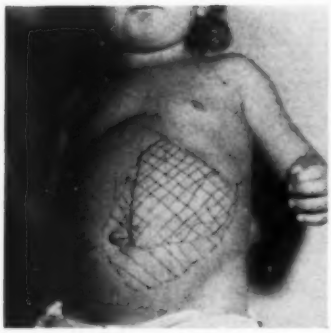

Fig. 2.—Blocks outline the spleen after the first transfusion. Lines show size of spleen after third transfusion.

Fig. 3.—Admission barium x-ray showing esophageal varices.

cnce of esophageal varices were considered indications for splenoportography (in the belief that there might exist splenic vein thrombosis causing portal hypertension). The results rise markedly and the platelet count continued to drop (see Fig. 1).

Surgery was finally decided upon. A physical examination showed no changes from the initial examination

Fig. 4.—Splenoportogram. Arrows point out aneurysmal proportions at the sight of bifurcation of the portal vein into right and left branches.

Fig. 5.—Close-up of area shown in Fig. 4.

were successful and they demonstrated the abnormality of the portal vein (Figs. 4 and 5).

One thousand cubic centimeters of whole blood was given because of continued anemia and bleeding. Despite these, the hemoglobin did not except that the spleen was now 9 cm. below the left costal margin and was tender. There were no ascites and no audible murmur over the hepatic area. The child was operated upon on Nov. 22, 1954, at which time the splenic artery was ligated (Figs. 6

and 7). Five days postoperatively, the platelet count had risen to normal and remained there for ten days at which time it started to drop again. Two weeks later, collateral veins were noted on the upper abdomen and the esophagus and the cardia (Figs. 8 and 9). Severe hematemesis with melena started after this study. The child then received 1,250 c.c. of blood in twenty-four hours. A Sengstaken tube (double balloon esophageal tube)

Fig. 6.

Fig. 7.

Fig. 6.—Forceps point to variceal abnormalities of the portal vein. There are further varices through the bifurcation of the portal vein intrahepatically which were revealed in the splenoportogram.

Fig. 7.—Spleen during procedure to ligate the splenic vein.

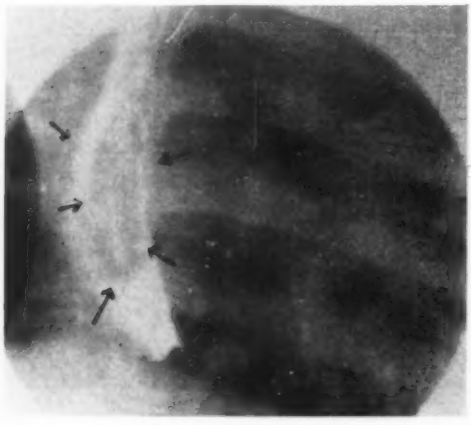

Fig. 8.

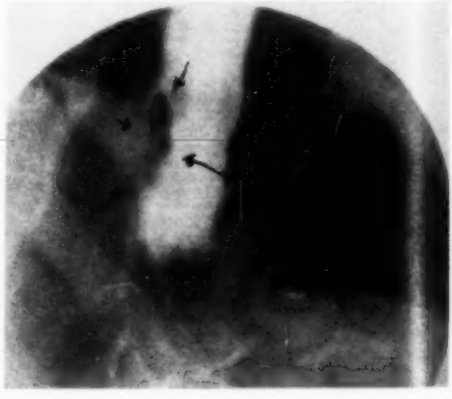

Fig. 9.

Figs. 8 and 9.—Esophageal varices after splenic artery ligation.

chest. The child was then sent home, under regular observation.

Five months later (April 25, 1955), a barium swallow study of the esophagus revealed numerous varices of was inserted. Two hours later the bleeding had stopped.

The next day, a laparotomy was performed in order to attempt a splenorenal shunt. The splenic vein

was found to be too small to permit the surgical procedure. Esophageal and gastric varices were located and ligated, and a splenectomy was performed by Dr. Koop in Children's Hospital in Philadelphia. After this operation, the platelet count rose to between 400,000 and 500,000 (see Fig. 1).

She remained in the hospital for ten days, and the following laboratory studies showed the white blood count to be 14,000; the red blood count to be 4,300,000; the hemoglobin to be 11 grams; and the platelets to be 383,000.

Since discharge, she has been seen monthly, and remains perfectly well. The blood count is normal and no hematemesis or melena has been noted to date.

DISCUSSION

Portal hypertension of the type herein described is asymptomatic until the onset of the first hemorrhage. When the physician first examines the patient, he is quite likely to miss the diagnosis. It is especially easily overlooked in children because of its rarity and the paucity of literature and study of this subject in the field of pediatrics.

In children, sudden hematemesis necessitates consideration of peptic ulcer, oropharyngeal bleeding, ingested foreign body, or blood dyscrasia. If these were eliminated, there would still be other possibilities to consider, such as Banti's syndrome, cirrhosis, Cruveilhier-Baumgarten syndrome, Gaucher's disease, or congenital abnormality of the blood vessels.

While demonstration of esophageal varices by x-ray or esophagoscopy is important, varices have been reported in this area in the absence of portal hypertension.[1]

If upper gastrointestinal x-ray studies suggest varices of esophagus or cardia, splenoportography should be performed so that the splenic and portal veins can be well defined.

Splenoportography is a helpful diagnostic procedure for evaluation in cases of portal hypertension. It gives a direct means of differentiating the many causes of portal block, intra- or extrahepatic. The former are amenable to splenorenal shunt therapy, a procedure that must be done with great precision and caution. Prothrombin determination is necessary in order to exclude hemorrhagic diathesis, a contraindication to splenography. A preliminary film should be taken to determine the size of the spleen. Local anesthesia is preferable, but due to the age of this patient, general anesthesia was used. A 17 gauge needle is inserted into the ninth intercostal space in the posterior axillary line. The patient may be tilted slightly to the right side while lying in the supine position. The point of the needle is directed upward and medially. When the splenic capsule is met, an increased sense of resistance is felt. As the organ is entered, there is a forceful reflux of blood into the syringe. Approximately 20 c.c. of 70 per cent Uroken or Diodrast is injected rapidly. X-ray exposures are started when three-quarters of the dye has been injected. Optimum results may be anticipated when using a rapid casette changer, preferably electrically controlled. The hand changer may be utilized. One thus obtains a vivid portrayal of the portal veins. Varicosities in the esophagus and the cardiac end of the stomach are depicted with clarity. In some instances of huge varicosities at

the cardia, one is able to differentiate these from a possible tumor of the stomach, although at the site of the bifurcation of the portal vein into its left and right branches, dilatation to aneurysmal proportions could be visualized. There was a marked lack of dye at the portohepatic junction itself. This was thought to be the result of the umbilical infection or possibly an infection affecting the ductus venosus. There were depicted huge varicosities at the cardioesophageal junction which later operation confirmed.

The splenography was repeated at laparotomy and the results duplicated. Splenoportography should be done when the stomach is empty, to lessen the possibility of inadvertently piercing it. It is inadvisable to inject the dye unless one is quite certain that the needle is intralienal. The patient should be encouraged to breathe in a shallow fashion in order to minimize trauma to the splenic pulp.[2, 3] The degree of hypersplenism and gastrointestinal bleeding is a guide to the necessity for prompt therapy. If at all possible, the portal pressure should be relieved. In 1928, McIndoe[4] advocated more attention to portal hypertension and to the principle of relieving the portal pressure by forming a fistula between the portal vein and the vena cava. Later, other workers felt that the use of the splenic vein would be better.[5] The procedure of choice in our case would have been splenectomy with a splenorenal shunt, but this is quite difficult in a child only 3 years of age with proportionately small veins. We felt, however, that splenectomy alone would be unsatisfactory as the child would still be left with hypertension and the portal vein would not be available for later anastomosis. The splenic vein would thrombose and then be useless for this purpose.

The literature by Kremish and associates[6] suggests splenic ligation for best results. In our case, a splenic artery ligation had no noticeable results. We feel that there are no promising therapeutic or surgical measures for correction of portal hypertension in the preschool age child.

For the bleeding emergency due to esophageal or cardial varices, the blood must be replaced. It then may be necessary to use balloon tamponage to stop the hemorrhage. After a Sengstaken tube is inserted through the nose, one bulb goes in the esophagus, the other in the stomach. After the pressure has been maintained for twenty-four hours, it was gradually decreased, and the esophageal balloon was deflated twice a day five to ten minutes' duration, at which time the head of the bed was elevated in order to permit blood that had collected in the esophagus to enter the stomach. After thirty-six hours, we were able to remove the tube completely. If, after forty-eight hours' arrest by tamponage, bleeding starts again, it is unlikely that the patient has portal hypertension due to extrahepatic portal block.[5] An emergency operative procedure, which has proved an efficient and lifesaving measure for control of hemorrhage, is the suturing of the esophageal varices directly through an esophagostomy. This procedure is now being employed extensively for patients who have immediate recurrence of bleeding after release of balloon tamponage.

In our patient, splenic enlargement became more marked after each

transfusion. This finding was also recorded by Smith and Farber.[1] Fifteen cases in which gastrointestinal bleeding occurred without other clinical signs showed that physical examination made immediately following hemorrhage may disclose no enlargement of the spleen. It is only after the bleeding has stopped or after the transfusion that the spleen became palpable.

Does umbilical infection as originally present in our patient lead to portal hypertension? Extrahepatic portal block and portal hypertension due to sepsis or thrombosis of the superior mesenteric, splenic, or thrombosis of the portal vein were mentioned by Heller[7] in 1904. Later, Turk[8] in 1912 and then Naegeli[9] in 1927 thought that a clinical picture such as splenomegaly without hepatomegaly, anemia, hypothrombopenia, or gastrointestinal bleeding may arise as the result of a cavernometous malformation in the terminal branches of the portal vein following thrombosis due to an umbilical infection. In 1930 van Creveld and Levy[10] wrote that for this pathologic picture to be present, there need not have been a severe antecedent umbilical infection.

We feel that umbilical infection may predispose to portal thrombosis. However, what the percentage of portal hypertension in patients who have had umbilical infection is, and how severe an infection would be necessary to predispose to portal hypertension, and how long after this infection would the portal hypertension develop are questions which remain unanswered today. In this case, it may well have had nothing to do with the previously mentioned umbilical infection, but may have been a congenital abnormality. The x-ray showed intrahepatic and extrahepatic angiomas, and the picture taken during the first operation clearly showed varices of the portal vein (Fig. 6).

After the onset of the splenomegaly, the attacks of gastrointestinal bleeding occur more frequently because of thrombopenia due to hypersplenism and the increasing portal hypertension. It appears from the communications of several investigators that bleeding often occurs immediately after or at the time of a period of fever. Enderlen[11] noted in 1914 that the congestion passes into the nasal veins and nasal bleeding then ensues if mediastinal and cervical collaterals are unable to transfer the blood to the mediastinum. Cauterization of the nasal veins does not help to stop the local bleeding.

CONCLUSION

A cavernous transformation of the portal vein was diagnosed by splenoportogram in a 3-year-old female child. Ligation of the splenic artery did not prove helpful. The portal hypertension was not relieved, nor was the blood picture changed. A splenorenal shunt was later attempted, but could not be done because of the small size of the veins. This would have been the ideal procedure. A splenectomy and ligation of the varices was done, after which the child's blood picture and general condition improved. This procedure should prolong the child's life.

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Early Traffic Problems

10:1:55. Whereas greatt inconveniences may accrew to the towne and inhabitants thereof, especially children, by persons irregular riding through the streetes of the towne, and galloping. Itt is therefore ordered that if any person shall bee seene to gallop through any streete of the town after this day, except upon dayes of military exercise, or any extraordinary case require, every such person shall pay two shillings, six pence, ...

2:2:58. Whereas by long and sad experience very many and greatt damages have accrued to this towne by swine, besides the many dangers that children have beene in of loss of life and limb, and elder people also of greatt hurt, by the unrulines and ravenousnes of swine. . . Itt is therefore ordered that henceforth every inhabitant in this towne that shall keepe any swine within this towne they shall constantly keepe up such swine in their owne ground. . . . .

29:4:58. Whereas many children and others are exposed to many dangers by Carts, either by being left carelessly in the streetes without their drivers, or else by the Carters riding through the towne in their Carts, Itt is therefore ordered that henceforth all horse-carts shall bee led by the carters with a rayne, and shall nott be left loose in any streete, but shall bee tyed to some place where they may not break loose. . . .

Boston Town Records 1634-1660, Boston, 1881.

June the 15th 1675 at a meeting of the Selectmen: it was ordered and agreed: that for the preventing off Hurtt to Children or els: that no person shall gallop any Horse: unlesse on extream necessity in the streets of Marblehead: upon the penalty of two shillings six pence. . . .

Marblehead Town Records.

ANEURYSM OF THORACIC AORTA IN AN INFANT TREATED BY RESECTION AND ARTERIAL HOMOGRAFT

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HOUSTON, TEXAS

ANEURYSM of the aorta occurring during infancy and childhood is rare and, furthermore, in none of the reported cases has successful surgical treatment been accomplished. In 1952 Javett and Kahn[5] reviewed fifty-three cases of aortic aneurysm reported in patients under 18 years of age and pointed out the difficulty in establishing the etiology of many of the lesions. Perhaps the most frequent cause for aneurysm at early age is subacute bacterial endocarditis and septicemia. Mitchell[6] recently collected five reported cases of mycotic aneurysm of the abdominal aorta, the patients ranging in age from 7 to 14 years, and reported another abdominal aneurysm in an 11-year-old girl who died of perforation and hemorrhage. Among the rarer causes for aneurysm are rheumatic fever, congenital syphilis, and tuberculosis by erosion of adjacent tuberculous lymph nodes into the aorta.

Congenital aneurysms of the aorta occur and possibly result from a deficiency in elastic tissue in the aortic wall. Gibson[3] reported a 16-month-old infant who died from perforation of an abdominal aneurysm in which the lesion was presumably congenital, although it also may have been mycotic. Congenital aneurysms may occur in conjunction with coaretation of the aorta or other vascular anomalies of the arch, and rarely occur as isolated lesions. Congenital aneurysms of the sinuses of Valsalva are unique, presumably representing a developmental defect of the bulbar and aorticopulmonary septa, and occur more frequently than any other congenital aortic aneurysms.[8]

Dissecting aneurysm of the aorta may occur during childhood as a result presumably of Erdheim's cystic medionecrosis, a unique pathologic entity characterized by mucoid degeneration and cyst formation or vacuolization of the media.[4, 7] Under certain circumstances the lesion may be hereditary and the most striking example is the heritable disorder known as Marfan's syndrome in which aneurysm of the ascending thoracic aorta is a characteristic feature in association with skeletal deformity, arachnodactyly, and ocular disturbances. In this syndrome dissecting aneurysm or aortic rupture may occur during childhood, resulting in death. Obviously trauma is still another possible etiological agent in formation of aneurysms of the aorta.

Recently we encountered at thoracotomy in an 11-month-old infant a large fusiform aneurysm of the dis-

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Aided in part by a grant from the Houston Heart Association.

tal thoracic aorta and proximal abdominal aorta which was considered to be a posterior mediastinal tumor or cyst prior to operation and which was successfully treated surgically.

CASE REPORT

R. M., an 11-month-old white male infant, was admitted to Texas Children's Hospital on Oct. 16, 1955, with a diagnosis of asymptomatic mediastinal tumor. Prenatal history was normal and labor was uncomplicated. Birth weight of the infant was 8 pounds 15 ounces. Soon after birth a mass about 3 cm. in diameter was noted in the sacrococcygeal region, and the mass was completely excised under general anesthesia. Recovery from operation was uneventful and a diagnosis of "chordoma" was made on microscopic examination of the specimen. Roentgenographic survey of the thorax and spine six months after the operation showed presence of a mediastinal tumor. He remained well and free of symptoms, however, until the present admission.

Physical examination revealed a well-nourished, active infant in apparent good health. Blood pressure was 110/70 mm. Hg in the right arm and pulses in all extremities were normal. There were no abnormal findings on examination of the thorax, heart, or lungs. The previous paracoccygeal incision was well healed, and there was no evidence of recurrence of the tumor locally or on rectal examination.

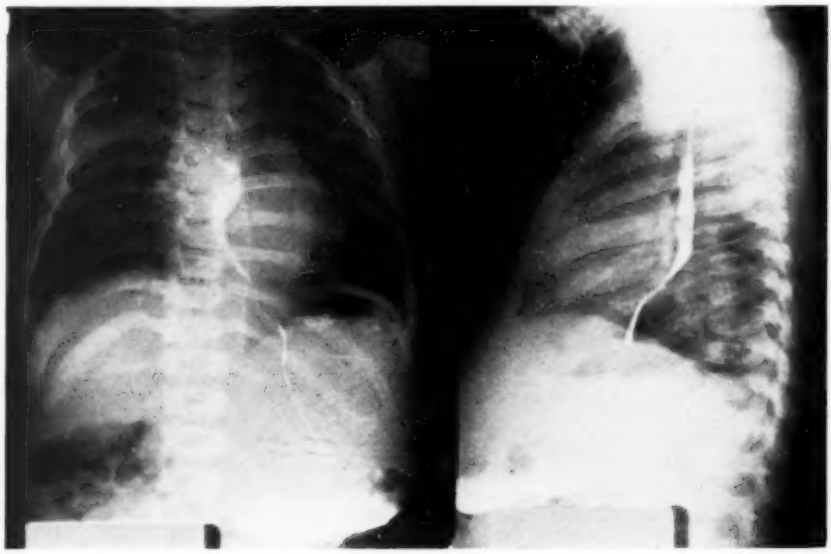

Fig. 1.—Roentgenograms of chest in posteroanterior and lateral projections with barium-filled esophagus, showing retrocardiac mass displacing the distal esophagus anteriorly and to the right. Ribs 5, 10, and 11 on the right are anomalous.

Laboratory studies revealed a normal hemogram and urinalysis. Serologic tests for syphilis on the patient and the parents were negative. Tuberculin skin test was negative. The electrocardiogram was normal.

Roentgenograms of the chest were made with the esophagus filled with barium and demonstrated a retrocardiac mass displacing the distal third of the esophagus to the left and anteriorly (Fig. 1). Ribs 5, 10,

and 11 on the right side were anomalous, but no other abnormalities were seen. Fluoroscopy indicated that the mass did not pulsate although there was a transmitted impulse from the adjacent left ventricle.

At operation on Oct. 17, 1955, a left posterolateral thoracotomy incision was made through the ninth intercostal space. The lung was retracted forward and the mediastinal pleura was divided parallel to the descending thoracic aorta. A fusiform aneurysm of the distal third of the thoracic aorta was discovered, measuring 7 cm. in length and 3.5 cm. in diameter (Fig. 2). The aorta proximal to the lesion was of normal caliber and measured 1.0 to 1.5 cm. in diameter. Distally the aneurysm passed through the aortic hiatus of the diaphragm. The aortic wall above the lesion was of normal texture and there was no evidence of inflammatory change or recent trauma.

The aorta above the aneurysm was mobilized and encircled with a tape for traction. In order to expose the aorta distal to the aneurysm it was necessary to dilate the aortic hiatus and retract the diaphragm downward. The aorta below the origin of the celiac axis was then encircled with a tape for traction. Several pairs of intercostal arteries were divided on the posterior aspect of the aneurysm.

A lyophilized segment of adult common iliac arterial homograft was reconstituted in warm saline solution and was of proper caliber to re-establish the aortic continuity in the infant aorta. The aorta above and below the aneurysm was occluded with noncrushing arterial clamps and the aneurysm was excised. The graft was sutured into the defect using continuous 00000 black silk arterial sutures (Fig. 2). The aortic clamps were released twenty-six minutes later and circulation was restored distally. Bleeding from needle holes ceased spontaneously and pulsation in the abdominal aorta and extremities returned promptly (Fig. 3). No other vascular anomalies of the aorta or heart were demonstrated. The mediastinal pleura was sutured over the homograft and the thoracotomy incision was closed with catgut and silk sutures, using an intercostal drain for underwater sealed drainage. At the completion of the operation the patient's condition was good.

On the morning following operation a mild nonfocal convulsive seizure occurred, followed by a brief period of generalized limpness, and a milder one occurred later the same day. Blood pressure at that time was approximately 150/60 mm. Hg. Serpasil 0.5 mg. intramuscularly was administered twice during the next

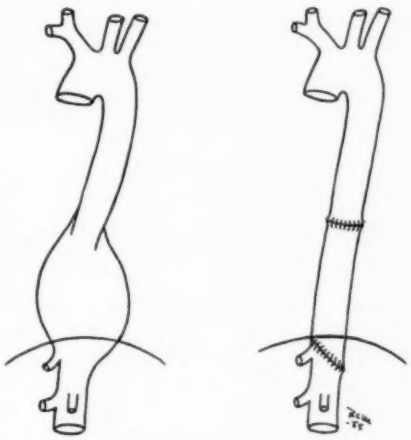

Fig. 2.—Drawing showing location of fusiform aneurysm arising in distal third of descending thoracic aorta and extending below the level of the diaphragm and the method of aortic repair with an arterial homograft after aneurysmectomy.

twelve hours and repeated orally in doses of 0.2 mg. for two days. Phenobarbital was given orally every six hours for the next five days and there were no further neurological manifestations. Blood urea nitrogen was mildly elevated to 31 mg. per 100 c.c. but two days later was 8 mg. per 100 c.c. One week after operation the patient developed a mild respiratory tract infection, vomiting, and diarrhea which was controlled by symptomatic therapy. The remainder of

the hospital course was uneventful and he was discharged from the hospital on Oct. 28, 1955, in good condition. Blood pressure returned to the preoperative level, and pulses in the lower extremities were normal.

Examination of the lesion revealed that the wall of the aneurysm measured 0.5 cm. in thickness (Figs. 4 and 5). The endothelium was yellow-gray and had numerous elevated plaques. Microscopic sections of the

Fig. 3.—Photograph made at thoracotomy, showing the iliac arterial homograft bridging the aortic defect after removal of the aneurysm. The anastomosis on the left is located just above the celiac axis.

Fig. 4.

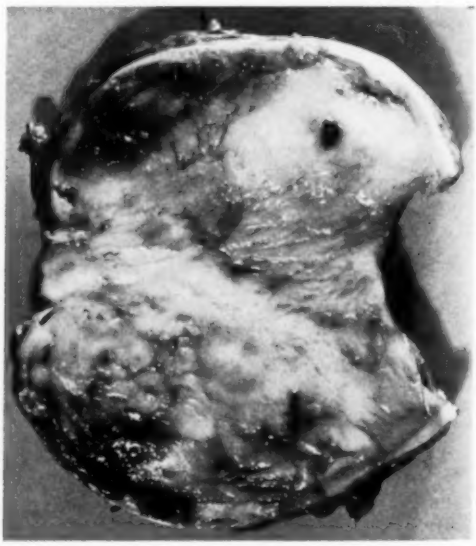

Fig. 5.

Fig. 4.—Photograph of aneurysm removed and measuring approximately 3.5 cm. in diameter and 6.0 cm. in length.

Fig. 5.—Photograph of inner lining of aneurysm revealing a yellow-gray surface with numerous elevated plaques.

lesion revealed destruction and splitting of the elastic and muscle layers of the media with replacement by fibrous tissue containing stellate fibroblasts. The fibroblastic tissue was located in a perivascular arrangement following the vasa vasorum where they penetrated the media from the adventitia. In addition to the perivascular response there was marked endothelial hyperplasia of the vasa vasorum. There was minimal inflammatory response with lymphocytes, plasma cells, and a few histiocytes in the perivascular spaces. Only a few polymorphonuclear leukocytes were demonstrated. The pathologic diagnosis was "mycotic aneurysm of the aorta."*

DISCUSSION

Before thoracotomy the diagnosis of posterior mediastinal tumor was made and because of its position and relationship to the heart and the esophagus, the possibility of a gastroenteric or esophageal duplication cyst was considered. Among other possible diagnoses were neurogenic tumor and coelomic cyst. Obviously aortic aneurysm could have been diagnosed if an aortogram had been done.

The exact nature and etiology of the aneurysm are not altogether clear. Although the pathologic diagnosis of mycotic aneurysm was made from the specimen on the basis of histologic evidence, the lesion also may have been congenital in origin. Support for this contention is gained from the absence of any previous episode of septicemia or infectious process in the infant to produce a mycotic process and also from the presence of other congenital anomalies, namely, the abnormality in the thoracic cage and the sacrococcygeal chordoma removed shortly after birth, indicating that the aortic lesion was also a developmental anomaly. On the other hand, one may postulate that the aneurysm was indeed caused by a low-grade infectious process which may have been present following removal of the retroperitoneal tumor at birth, accounting for the histologic appearance resembling a mycotic aneurysm.

During the past five years efforts at surgical treatment of aortic aneurysm by resection of the lesion with restoration of continuity have made possible the cure of aortic aneurysms where previously treatment was only palliative at best.[1, 2] At present for saccifform aneurysms of the aorta where the neck of the lesion is relatively small, tangential excision and lateral aortorrhaphy may be satisfactory. Fusiform aneurysms which involve the entire aortic circumference require segmental aortectomy. In this instance insertion of an aortic or arterial homograft is required to re-establish aortic continuity.[2] Lyophilized or freeze-dried arterial homografts have been used for this purpose and follow-up observations made several years later indicate that the grafts continue to function satisfactorily for prolonged periods, maintaining a surprisingly normal histologic appearance. Although aortic homografts have been used in children following resection of unusual coarctations, this case is the first infant to have an aortic aneurysm successfully removed with aortic graft replacement. The question immediately arises in this case in regard to the ultimate fate of the graft through the years and the rate of growth in relation to growth of the adjacent aorta. Obviously frequent subsequent examinations should be done to detect any tendency to dilata-

*Dr. Harvey S. Rosenberg, Pathologist, Texas Children's Hospital.

tion or occlusion of the graft so that the graft subsequently may be replaced by a larger homograft if the necessity arises.

SUMMARY

Aneurysm of the aorta in infancy and childhood is rare, and successful surgical treatment has not been previously recorded. A case of an 11-month-old infant is reported with a large fusiform aneurysm of the distal thoracic aorta which was either mycotic or congenital in origin. The aneurysm was resected and the aortic segment replaced by a lyophilized arterial homograft, with ultimate recovery of the patient.

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On Whooping Cough

We have already previously spoken of the beginning of summer. At the end of summer almost the same diseases flourished as before. The summer was glowing and burning hot. Boys four months old, ten months old and a little older were attacked by fevers, which carried countless off. Especially that common cough, which is generally called quinta or quintana and which we have mentioned before. Its symptoms are serious. The lung is so irritated that, in its attempt by every effort to cast forth the cause of the trouble, it can neither admit breath nor easily give it forth again. The sick person seems to swell up and as if about to strangle holds his breath clinging in the midst of his jaws.

Why it is commonly called quinta, is not without doubt. Some think the word is a manufactured one through onomatopoiea, from the sound and the noise which those so coughing emit. Some do not seek its source hence, but think that the cough is called quintana in Latin because it recurs at fixed hours—a fact which experience proves to be true. For they are free from this annoyance of coughing sometimes for the space of four or five hours, then the paroxysm of coughing returns, sometimes so annoying that the blood gushes out of the nostrils and the mouth by the violence. Very frequently the belly happens to be upset. I have not read any author who writes about this cough.

GUILLAUME DE BAILLOU, 1578.

ON THE NATURE OF THE "STENOSIS" IN CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

Report of a Case of Pyloric Stenosis in Which a No. 14 Catheter Was Inadvertently Passed Through the Pyloric Sphincter

Jacob J. Wiener, Lieutenant (MC) USNR, Joseph M. McGinley, Lieutenant Commander (MC) USNR, and Donald K. Adler, Lieutenant (MC) USNR

THE etiology and pathogenesis of congenital hypertrophic pyloric stenosis remain as puzzling today as when first described. Although the disease has been recognized as early as 1717, and much progress has been achieved in its early recognition and treatment, no satisfactory answer has yet been found to explain the nature of the stenosis, or the factors producing the hypertrophy of the pyloric muscle.

Our recent experience with a case of pyloric stenosis may help elucidate some of the problems involved.

CASE REPORT

Michael D., aged 4 weeks, was admitted to the St. Albans Naval Hospital on Dec. 13, 1955. His birth weight was 8 pounds 1 ounce. He had done well for the first three weeks of his life, but during the fourth week had been losing weight. On admission, the infant weighed 8 pounds four ounces. He had been vomiting all his feedings in a projectile manner, and had had no stools for the past three days. The infant was mildly dehydrated, and had a respiratory rate of 30 per minute. Peristaltic waves were observed and could be easily elicited. A mass could be felt just below the liver edge, but this finding was not confirmed by all observers. The infant was given nothing by mouth, and parenteral fluids were administered. On December 14, the morning following admission, 10 c.c. of Lipiodol was offered to the infant in preparation for x-ray studies. He vomited it, and, in order to introduce the dye, a No. 14 catheter was passed. The tube was inadvertently passed beyond the pyloric sphincter. X-ray studies were interpreted as follows:

"Examination discloses a catheter through the esophagus, stomach, and passing into the jejunum. Lipiodol was instilled and fills out the stomach which does not appear noteworthy. The tube passes into the duodenum which precludes obstruction. Films made in three to four hours disclose considerable residue in the stomach. Opaque material is seen in the small intestine as well as what appears to be jejunum. It is possible that the tube occluded the pylorus and retarded progress. Further study is recommended and will be done. Impression is that there is no definite organic obstruction in the distal stomach or duodenum. Obstruction in the small bowel distal to these sites is to be excluded."

X-ray studies about twenty-four hours later were read as follows:

"Further examination discloses scattered globules of opaque material in the stomach and in the intestinal tract.

From the Pediatric Service of U. S. Naval Hospital, St. Albans, N. Y.

The opinions and assertions contained herein are the private ones of the writers, and are not to be construed as official or reflecting the view of the Navy Department or the Naval Service at large.

This suggests some partial impedance to the passage, which may, however, be functional."

As a result of the x-ray findings the diagnosis of pylorospasm was entertained. The infant was given atropine 1/1,000 gr. subcutaneously every six hours, phenobarbital 1/8 gr. subcutaneously every six hours, and was offered 10 c.c. of glucose in water every two hours. He did not retain any of his feedings. Vomiting persisted even when thickened feedings and feedings in the upright position were tried.

On the basis of the clinical picture and the hospital course, it was decided that the infant be explored for pyloric hypertrophy. The operation was performed on December 17, and a moderate pyloric hypertrophy was found. Pyloromyotomy was performed. Postoperatively the infant vomited only once. His feedings were gradually increased and he was discharged home in good nutritional status, weighing 8 pounds 12 ounces six days following operation.

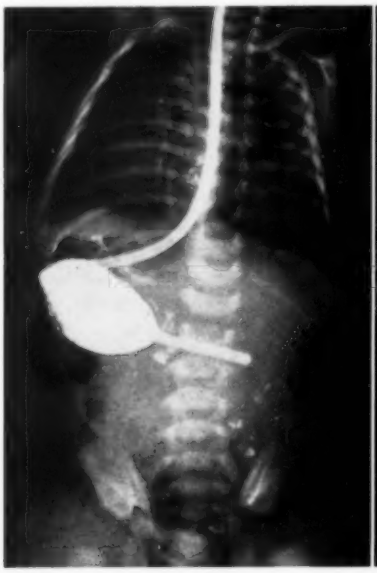

Fig. 1.

Fig. 2.

Fig. 1.—Posteroanterior view of the abdomen. The tube is in the duodenum; the Lipiodol has been recently inserted.

Fig. 2.—Lateral view of same patient in Fig. 1.

DISCUSSION

There is no agreement as to when and why the muscle in the pyloric canal thickens. Some investigators[1-3] believe the hypertrophy of the pylorus to be present before birth, and to be responsible for the narrowing of the pyloric lumen. According to others,[4] the hypertrophy does not appear to be present at birth and is only a later development. It is postulated that the hypertrophy is secondary to a reflex spasm, the true neurological nature of which has not yet been elucidated, since no abnormality of nerve supply has been demonstrated. The theory that the muscular anomaly is congenital is supported by the fact that children dying shortly after the appearance of clini-

cal symptoms already show a degree of hypertrophy which could hardly have arisen in such a short course of illness. In a study of 1,000 normal infants, of whom five eventually developed pyloric stenosis at the age of 3 weeks, Wallgren[4] could find no radiologic signs of the condition in x-rays taken periodically from the time of birth until the onset of illness. This led him to the conclusion that, in these cases, the muscular hypertrophy was not congenital.

The term "stenosis" suggests that it is the anatomical reduction in lumen affected by the hypertrophied muscle which is the cause of the vomiting. This is to differentiate the condition from pylorospasm, where it is the tone of the sphincter (a disturbance of the nervous mechanism) which underlies the condition. And yet, pyloric stenosis is different in nature from other congenital stenoses in the gastrointestinal tract. Unlike the congenital stenoses, the pyloric stenosis does not cause vomiting at birth, but much later. In our case the pyloric "stenosis" permitted the passage of a No. 14 catheter. Logically, therefore, we must question whether the anatomical decrease of the lumen is the main cause of vomiting in pyloric stenosis or whether there are other causes operating, which, even with a relatively wide lumen, will bring about vomiting and delayed emptying of the stomach.

Pathological studies[4] show the lesion to consist of hypertrophy of the circular layer, and, to a lesser degree, of the longitudinal layer of muscle in the wall of the pyloric sphincter. The mucosa is edematous and infiltrated by inflammatory cells. The edema eventually leads to a decrease in the lumen of the pyloric canal. It is quite conceivable that, in the early stages, the inflammation and edema in themselves will cause vomiting even before effecting a marked decrease in the lumen of the pyloric canal. An inflamed mucosa without marked obstruction will not permit passage of food, while a wide tube can still be pushed through.

SUMMARY

A case is presented in which surgical treatment of a true pyloric stenosis was delayed because a large rubber catheter was passed through the pylorus. This is further evidence of the fact that functional inhibition of normal peristalsis occurs due to edema alone and a true anatomical stenosis in the mucosa need not be present.

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CONGENITAL ATRESIA OF THE ILEUM IN TWO BROTHERS

Case Report

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Haifa, Israel

SOME of the important congenital conditions leading to intestinal obstruction in the newborn infant have a genetic factor. These include fibrocystic disease of the pancreas,[1] congenital megacolon,[2] and agenesis of the myenteric plexuses.[3] The importance of a family history in the clinical diagnosis of meconium ileus has been stressed,[4] so that the occurrence of meconium ileus or fibrocystic disease of the pancreas in a sibling is a valuable diagnostic aid.

This discussion records congenital atresia of the ileum in two brothers and discusses briefly the prognosis for further children. In the preoperative differential diagnosis of the second case, exact pathological details of the first patient were not immediately available. The history of a fatal neonatal operation for intestinal obstruction led us to favor meconium ileus as the probable diagnosis in both cases. It is generally accepted that, with the possible exception of congenital megacolon, all cases of neonatal intestinal obstruction should be given the chance of immediate surgery. Any facts which may assist in the preoperative diagnosis are worthy of record.

From the Pediatric Departments of the Rothschild and Government Hospitals.

CASE REPORTS

Family History.—The father was born in 1914 and had three healthy sisters. The mother was born in 1923 and had a brother and sister, both of whom were healthy. The parents were born in different parts of Poland. There was no known consanguinity and no known case of neonatal death in their families. They married in 1946 and a healthy male child was born in 1950. There were no miscarriages.

Case 1.—Following an uneventful pregnancy and labor a (second) full-term male child was born on July 20, 1953. Eight hours after birth, feces and urine had not been passed and the infant repeatedly vomited bile-stained fluid. Physical examination revealed slight cyanosis about the mouth and a markedly distended abdomen with meteorism. An x-ray film of the abdomen showed fluid levels, suggesting intestinal obstruction.

Laparotomy was performed. The stomach, duodenum, and part of the jejunum were grossly distended and appeared to end blindly without direct connection with the ileum. The ileum and large intestine were very small in caliber. There were numerous adhesions between the intestinal loops. Jejunostomy was performed, but the infant died the same day.

Post-mortem examination revealed marked dilatation of the jejunum and duodenum, with fresh hemorrhages of the mucosa. The colon was narrow

and contained thick white meconium. The peritoneum and serotum showed hemorrhages. The lower lobes of the lungs were atelectatic. Microscopic sections from various bowel segments showed no abnormality, and the myenteric plexuses were present.

CASE 2.—Following an uneventful pregnancy and labor, a (third) full-term male child was born on Dec. 27, 1954. No stool was passed during the first three days and he vomited dark green fluid. He was then transferred from a nursing home to a pediatric department. On examination, the general condition was good except for slight cyanosis. The abdomen was markedly distended, with prominence of the veins around the umbilicus. The outline of the distended intestines was seen through the abdominal wall. Percussion elicited a tympanitic note, and loud peristaltic sounds were heard on ascultation. An x-ray film of the abdomen showed gross distention of intestinal loops. A barium enema filled all the large intestine, which appeared very narrow. Full details of the previous child were unavailable and a diagnosis of meconium ileus was considered probable.

Laparotomy was performed. The small intestines were distended. There were numerous adhesions, similar to those seen in peritonitis, between the swollen loops. The large bowel was narrow, and the cecum and transverse colon appeared to be rotated around one another. Attempts to separate the adherent loops of bowel failed, and the infant's condition deteriorated during the operation. The abdomen was closed and the infant died ten hours later.

Post-mortem examination revealed atresia of the distal third of the ileum with marked dilatation of the proximal ileum. The colon was hypoplastic. Microscopic sections from various segments of the bowel showed no abnormality. The myenteric plexuses and pancreas were normal.

DISCUSSION

The congenital malformation in each child was almost identical in both site and type—atresia of the ileum. There was no evidence of defective innervation of the bowel or of pancreatic fibrosis. Although perforation of the bowel was not present, the peritoneal adhesions in each case were probably secondary to the intestinal obstruction itself.

Congenital stenosis and atresia of the bowel are rare. Twenty-six cases were noted among 6,000 autopsies performed at the Hospital for Sick Children, Great Ormond Street.[5] In their report on abnormalities observed during the first six days of life among 8,176 live-born infants, Harris and Steinberg[6] recorded three cases of intestinal obstruction—one case each of duodenal atresia, fibrous band, and gut malrotation. Louw[7] recently published a comprehensive review of congenital intestinal atresia and severe stenosis in the newborn infant and estimated an incidence of these conditions of at least 1 in 3,000 births. In the family recorded by us, the presence in two out of three siblings of identical malformations with such an incidence suggests a genetic determination.

The pediatrician is faced with the task of advising the parents on the risk in a future pregnancy. Murphy[8] has stressed the greatly increased danger in families with one malformed child of duplication in subsequent births of the defect present in the first malformed child. Genetically, in the family recorded by us, it is possible that the condition may be due to a recessive gene. It is, however, surprising that a malformation with such an incidence should have

occurred in two siblings of parents not consanguinously related, as it is an axiom in human genetics that the rarer the gene, the more likely for it to be limited to the children of consanguinous marriages.[9] If the malformation is due to a recessive gene, the chance of the next child being affected is theoretically one in four.

This problem is of marked practical importance in such a family. Koop[10] states that the mortality in neonatal obstruction is roughly directly proportional to the patient's age and that distal lesions of the small intestine are increasingly more difficult to manage. With such a family history, a maximum of planned surgical and pediatric supervision can be commenced immediately after the birth of the next born infant, so that early surgical exploration can be performed if necessary. Radiological investigations could be dispensed with, and early surgery attempted before the infant's general condition deteriorates.

SUMMARY

In two of three male siblings, congenital atresia of the ileum caused fatal intestinal obstruction. The genetic implications are briefly discussed.

We are indebted to Dr. H. Harris of the London Hospital Medical School and to Dr. L. Sachs of the Weizman Institute of Science for advice on the genetic aspects; to Dr. B. Ostrowski and Dr. J. Bar-Chay for permission to report these cases; and to Dr. B. Gelei, Dr. D. Peyser, and Dr. D. Ehrlich for their help.

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MALIGNANT THYMOMA (LYMPHOCYTIC TYPE)

James I. Hudson, Jr., Captain, USAF (MC),* Francis P. Catanzaro, Captain, USAF (MC), A. F. Bloodworth, Captain, USAF (MC), and O. W. Topp, M.D., Lake Charles, La.

A CASE of a 4-year-old white male with a large, malignant thymoma, simulating a bilateral pneumothorax with atelectasis, is reported.

This tumor, by its position, size, and x-ray appearance, mimicked a bilateral partial atelectasis with pneumothorax. The x-ray picture, together with the clinical appearance of marked cyanosis and orthopnea, confused the clinical diagnosis. The diagnosis was made while attempting to massage the heart after the patient had died during bronchoscopy.

In reviewing the literature we find a similar case reported by Bernstein and associates,[1] in 1951, where a large, firm, mediastinal, thymic tumor was mistaken for a pericardial effusion.

Since mediastinal tumors are not often considered in the differential diagnosis of atelectasis and pneumothorax, this case is being reported. It is apparent from the description and x-ray films that this tumor caused confusion in diagnosis because it enveloped the heart and tracheal bronchial tree, and yet did not show the usual eccentric enlargement seen with mediastinal tumors.

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CASE REPORT

This patient (Reg. No. 8215), a 4-year-old white male, was admitted on Aug. 19, 1955, with the chief complaint of progressive orthopnea which began five days prior to admission.

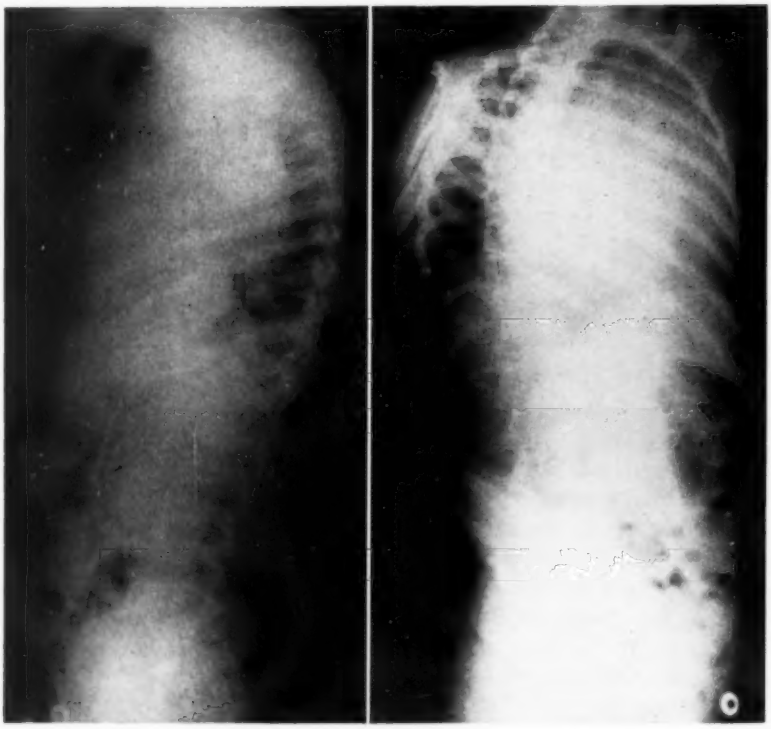
Family history revealed that the patient's mother was subject to frequent attacks of asthma with considerable wheezing. The patient himself had always enjoyed relatively good health. He had a past history of chronic, draining, bilateral otitis media. There was no history of antecedent cardiac disease or pulmonary difficulty. He had never had any cough or wheezing prior to this illness. Five days prior to admission the patient developed a slight cough and a slight temperature elevation and became anorexic. Three days thereafter, because of progressive difficulty with breathing, and wheezing, he was first seen in our dispensary.

Examination at that time revealed a red pharynx and red tonsils, and râles were heard throughout the anterior chest. Bilateral inspiratory wheezes were heard. Diagnosis at that time was acute tonsillitis and possible bronchopneumonia. Admission was advised, but the parents refused. Patient was started on penicillin therapy.

Early on the morning of admission he returned to the dispensary because of the progression of the dyspnea and wheezing. He was given 0.4 c.c. of Adrenalin, subcutaneously, and returned later in the morning because this had no effect. He was admitted at this time.

Physical examination revealed a temperature of 100.2° F. The child

A.



B. *C.*

Fig. 1.—Roentgenograms of the chest demonstrating a large opacity extending anterior to the trachea, with associated tenting and elevation of the right diaphragm and shift of the trachea to the right. The opacity was proved to be a thymic tumor obscuring a bilateral atelectasis. *A*, Erect posteroanterior view; *B*, left lateral view; *C*, right anterior oblique view.

was well developed and well nourished, but in moderately severe respiratory distress. He became severely dyspneic whenever he lay down. The expiratory phase was prolonged. There was a moderate amount of brown, thick discharge exuding from both external ear canals. Percussion note over the chest seemed hyperresonant posteriorly. Good breath sounds were heard posteriorly. Breath sounds were diminished anteriorly. No wheezes were heard, nor were there audible râles. The trachea was not felt to be shifted. It was difficult to percuss the cardiac outline. It was not felt that the heart was enlarged. The heart sounds were distant. There was a rapid cardiac rate, regular rhythm, no murmur. Liver and spleen were not palpable. Patient's color was good. There was no cyanosis and no obvious neck venous distention.

Chest fluoroscopy on admission revealed a large, irregular density throughout the medial portion of the thorax. This area pulsated with the heartbeat on the left side, and seemingly moved with respiration on the right side. No definite cardiac border could be made out, nor could definite pulmonary markings be ascertained on either side of the medial mass. The chest fluoroscopy gave the impression of a partial bilateral atelectasis, with possible pneumothorax, bilateral, without mediastinal shift, cause undetermined.

Chest x-rays (Fig. 1) confirmed the fluoroscopy findings, but shed no light on the specific etiology of the findings. Some lung markings were apparent on either side of the mid-thoracic mass.

After the patient was admitted to the ward and placed in an oxygen tent he showed some improvement. A No. 20 needle was inserted in the left posterolateral chest in an effort to ascertain the presence of pneumothorax. No air was obtained upon entry into the thoracic cavity.

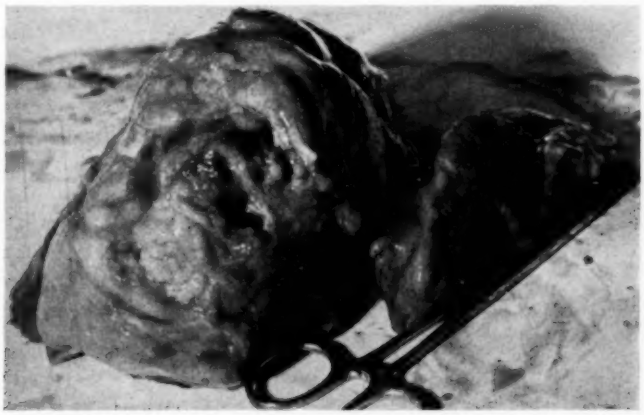


Fig. 2.—Tumor mass showing encirclement of trachea and main bronchi.

Later in the afternoon, because of the possibility of a bilateral atelectasis secondary to intrinsic blockage of the main bronchus, it was felt that the patient should be bronchoscoped.

The patient was prepared for bronchoscopy, but during the initial phase, as the laryngoscope was being passed, he suddenly stopped breathing.

An emergency tracheotomy was performed. This was extremely difficult because of profuse bleeding, presumably due to considerable ve-

nous congestion in the neck. An airway was maintained, the patient's trachea was suctioned, and he seemed to improve temporarily. However, approximately fifteen minutes following this procedure he again stopped breathing and no heartbeat could be felt or heard.

At this juncture an emergency thoracotomy was performed in an effort to stimulate and massage the heart. When the left thorax was opened, a large, rubbery, white tumor mass was found completely overlying the heart and the great vessels, and filling the greater part of the chest. Efforts at cardiac massage and stimulation were to no avail, and the patient was pronounced dead.

Bronchoscopy, post-mortem, revealed the carina to be flat, and both main stem bronchi to be considerably narrowed and almost occluded.

Pathological Findings.—Gross: A mass (Fig. 2) of gray-white, soft, rubbery tissue, measuring 15 by 12 cm. On the posterior surface was the impression of the heart. Attached were the lungs. The cut surfaces of the mass were lobulated and the anterior surface was encapsulated. The tissue varied from soft to leathery, and was homogeneous, pink-white, with focal areas of hyperemia. Attached along one margin was a portion of lung tissue which showed marked atelectasis and congestion. The tumor surrounded and involved the aorta and great vessels, the pericardium, and hilum of the lung. No lymph nodes or pulmonary neoplasms were found.

Microscopic: Multiple sections revealed the tumor to be composed of small round cells with well-defined nuclei, but ill-defined and scant cytoplasm, growing in a lobulated pattern resembling small lymphocytes in detail. No Hassall's corpuscles were noted. Invasion of the adventitia of the great vessels, as well as the lung tissue, in relation to the hilum was noted. The alveoli exhibited collapse, and edema fluid was present in the bronchi. Other sections revealed invasion of the pericardium by similar tumor cells.

DISCUSSION

The clinical course which this patient displayed is typical of those cases described in children. The tumor itself is either extremely rapid growing, or possibly it grows in such a fashion and direction that only late, when it has expanded to completely encircle all the mediastinal structures and surrounds the vessels and trachea, does it give rise to symptoms.

Gross[2] describes two patients who entered the hospital in extremus. In both cases a tracheotomy was performed with the hope of giving some relief prior to the institution of x-ray treatment. Even with the improvement of the airway by insertion of a tracheotomy tube, the vascular disturbances were such that death promptly followed and there was no opportunity in either case to institute x-ray treatment.

This tumor was considered an invasive, malignant thymoma. It demonstrated implantation in lung tissue. The frequency of thymic cancer is low when the reported cases of thymoma are screened by strict criteria. The numerous case reports include other tumors, such as lymphomas and teratomas. The number of invasive malignant thymomas reported were thoroughly reviewed by Morgan and Dudley[3] and a total of forty-four cases appeared to fit the pathological criteria of invasiveness and cellular type.

In thirty-two of the forty-four cases, data for age and sex were given, the youngest being 10 years old, and the oldest 71. Myasthenia

gravis was associated definitely with twenty-five of these cases, and questionably associated with four of them. Seven cases had no association whatsoever with myasthenia gravis.

By history, our patient showed none of the symptoms attributable to this disease (myasthenia gravis).

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Humility and the Physician

After all things are considered and weighed, in this and other Chirugicall Discourses that are publick, and they compared without success in Practice, we shall soon find cause of lamenting our own weakness and inability in the carrying on of so great a work as the recovery of Mankind out of those many Distempers to which various Misfortunes, and many repeated successions of Intemperance, and other Accidents both without and within, have betrayed us for so many ages together . . . For my part, I have thought it no disgrace to let the world see where I failed of success, that those that come after me may learn what to avoid: there being more of instructiveness often in an unfortunate case than in a fortunate one; and more ingenuity in confessing such misfortunes which are incident to mankind, and which have attended all my Brethren as well as myself, and will attend thee also, Reader, if thou undertake the employment. Thou wilt also learn one necessary piece of Humility, viz., not to trust too much in thy own judgment, especially in difficult cases, but to think fit to seek the advice of other Physicians or Chirurgeons, whose long experience hath enabled them to assist thee in preventing the Accidents, and encourage thee to go on in the work, or forewarn thee of the danger. After thou hast thus defended thyself from the censure of Rashness, proceed boldyly, and let thy sincerity in thy acting be thy warrant to hope for God's Blessing on thy endeavours; and if these Papers prove any advantage to thee in them, remember with kindness the Labours of

Thy Friend and Servant,

RICHARD WISEMAN (1676)

Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

First Admission.—A white girl aged 11 years 10 months, who, prior to admission here, was studied extensively at an outside hospital for pallor, weakness, weight loss, and splenomegaly of one year's duration. There was no history of previous hepatitis or familial blood dyscrasia, and no neonatal or umbilical infection. She was transferred here because of x-ray findings suggesting esophageal varices.

Physical examination upon admission revealed a well-developed, poorly nourished, pale child appearing chronically ill. Temperature was 99.2° F., pulse 80, respirations 20, blood pressure in left arm 110/70. The only abnormal findings were abdominal. The abdomen was soft and mildly protuberant. The liver border was palpable 2 fingerbreadths below the right costal margin. There was a large, firm, nontender, slightly movable, left upper quadrant mass that moved with respiration. Peristalsis was normal. There were no other masses. There were no abnormal superficial veins and no hemorrhoids.

Laboratory studies here were as follows: hemoglobin 9.0 grams, red blood cells 3.3 million, white blood cells 6,000 to 9,200, and hematocrit value 29 per cent. Smear of the peripheral blood disclosed hypochromic, slightly microcytic anemia, with a Cooley's trait, slightly decreased platelets, and 3 per cent reticulocytes. The sedimentation rate was 34 (corrected). A Hinton test was negative. Urinalysis was normal. Liver function studies revealed thymol turbidity 10 units, thymol flocculation 4 plus, cephalin flocculation 4 plus, bilirubin normal, prothrombin time normal, urobilinogen positive (1:64). Stool guaiac tests ranged from 1 plus to 3 plus on four occasions, and the bone marrow examination was consistent with intermittent blood loss and blood destruction.

The patient had never noted any gross bleeding from the gastrointestinal tract. She continued to run a fluctuating fever (100 to 101° F.) throughout her ten-day hospitalization. Surgical treatment was considered but deferred.

She was given a period of bed rest with bathroom privileges and special diet at a convalescent home. Return of temperature and liver function toward normal were to be the criteria for measuring her therapy. She became afebrile, and remained so, and gained weight with an improvement

of appetite and decrease of anemia. Her liver function tests continued to be markedly abnormal with little actual change, although the van den Bergh reaction was normal. After two months she went home on a similar regimen for about six weeks before readmission to the hospital.

Second Admission.—Physical examination showed absence of the previously noted pallor, the liver was still one fingerbreadth below the costal margin, and the spleen still reached almost to the left iliac crest. The prothrombin time was 16.1, with a control of 13.9 seconds. A Bromsulphalein test after forty-five minutes revealed 72 per cent retention. The serum protein was 7.2 grams per cent; the hemoglobin, 11 to 12 grams per cent. Barium swallow again demonstrated esophageal varices but the stools contained no occult blood. Liver function studies were little changed. On the tenth hospital day splenectomy with end-to-side anastomosis was performed. Immediately preoperatively a percutaneous splenoportal venogram was carried out. Splenic vein pressure at operation prior to anastomosis was recorded at 285 mm. of water. Because of a demonstrated partial defect in her prothrombin accelerating factor, she was given 500 c.c. of fresh whole blood on the day before operation and 250 c.c. of fresh frozen plasma immediately preoperative. The operation and early postoperative course were uneventful, and she was discharged home on the eleventh postoperative day.

Since that time she has been quite well clinically, with no fever, jaundice, or gastrointestinal bleeding. Since the first few months of restricted physical activity she has played and kept up with the other children. Liver function studies one month ago were: thymol turbidity 20.0; thymol flocculation 3 plus; cephalin flocculation 3 plus; 1-minute serum bilirubin 0.32 mg. per cent; total serum bilirubin 0.90 mg. per cent. Hematologic studies were normal.

DISCUSSION

DR. CHILTON CRANE.*—This patient was referred here because of x-ray findings of esophageal varices. That would suggest that the pediatrician taking care of her thought that a surgical splenorenal shunt should be considered. An immediate splenectomy was not performed. It would have done her very little good in the long run, from the point of view of her bleeding, and would have made her splenic vein unusable for a future shunt. The fact that she was pale and chronically ill means she was certainly not a good candidate for a large surgical procedure. There were no abnormal superficial veins and no hemorrhoids. The appearance of superficial venous channels is tremendously variable but this particular child was not using these venous pathways for collateral flow. We notice in the laboratory data that she had a well-established hypochromic and slightly microcytic anemia, which was secondary to bleeding. The white blood cells were normal and her platelets were only slightly decreased. This suggests that even though her spleen was considerably enlarged, this had not been of sufficiently long duration to give her the signs and symptoms of hypersplenism, for she was

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not destroying the platelets, red cells, and white cells to any measurable degree. The thymol turbidity and flocculation and the cephalin flocculation tests were all elevated, suggesting a quite marked liver cell damage. On the other hand, the serum bilirubin was normal. This is very encouraging, for patients with severe liver disease who are not jaundiced are much better candidates for surgery than if they have either clinical jaundice or an elevated bilirubin. The urinary urobilinogen was elevated to 1:64. This indicates an inability of the liver to re-excrete absorbed urobilinogen, so that urobilinogen spills over in the urine. She never had a true hematemesis or tarry stools—this would fit in with the fact that her portal pressure at operation was 285 mm. of water. Dr. Child[1] has pointed out that a portal venous pressure of 300 mm. level of water is a critical one for esophageal varices, in that patients with pressure readings of 340 to 360 mm. really bleed and continue to bleed; but patients whose portal pressure is in the region of 240 to 280 mm. of water are much more likely to ooze a bit and not have really massive hemorrhage.

Surgical therapy at that admission was deferred because of severe liver cell damage, and in the hope that the patient could be improved clinically before bringing her back for surgery. At the convalescent home she became afebrile and remained so. We note during her first admission that she had a temperature between 100° and 101° F., but we have no real clue as to its cause. In any event, her fever disappeared, her appetite improved, and she began to gain weight, all excellent signs in a patient with this type of liver involvement and gratifying to have occur before undertaking surgery. Her anemia also improved. I judge that she simply stopped bleeding. Her liver function tests continued to be markedly abnormal, with little actual change although the van den Bergh reaction was normal. They gave her two more months at home, so that about three and one-half months intervened between her first admission and her second. On physical examination at the time of her second admission, she looked better. The liver still was enlarged, as we would expect, but perhaps a little smaller. The spleen was unchanged. The Bromsulphalein test after forty-five minutes showed 72 per cent retention, which would indicate quite advanced liver damage. Yet in patients with portal obstruction or in patients who have already had a shunt, the Bromsulphalein test is a little unfair because they will show more retention than patients without portal obstruction or that have not had a shunt because of their inability to absorb the dye via the portal vein. We notice that her serum protein level was excellent, 7.2 mg. per cent, which is most encouraging. I would guess that the albumin was 3.8 grams per cent, or something of the sort, a very favorable level. It has been pointed out, chiefly by Dr. Robert Linton,[2] who went over a number of his old cases and discovered that the patients who did not do well had albumin under 3 grams per cent, whereas, in general, those individuals who survived the shunting procedure and continued on into the postoperative period almost always had serum albumin levels higher than that. Dr. E. J. Jahnke, at the Walter Reed

Hospital, has operated upon a good many patients with quite low serum albumin levels which he tends to ignore. The Army patients at Walter Reed Hospital have a little different brand of cirrhotic liver, since many of the cases are young men with hepatitis or posthepatitic cirrhosis and apparently they stand the procedure better, although in the long range they probably are not going to do as well from the point of view of their liver disease alone.

On the tenth hospital day splenectomy with an end-to-side splenorenal anastomosis was carried out. Immediately preoperatively a percutaneous splenoportal venogram was done, which sounds like a good idea. In adults who can hold their breath and thus keep the spleen from moving, there is very little danger. On the other hand, in children, particularly under anesthesia, one might tear the spleen, but with immediate surgery being planned anyway, one would not worry. From such a procedure one might learn the location of the thrombus, whether it is in the splenic vein or farther back in the portal vein. The latter does not seem likely in this particular patient. Yet in any patient with advanced cirrhosis and with considerable intrahepatic venous obstruction, the portal blood flow finally becomes slow and even may reverse itself, so that thrombosis of the distal portal vein does occur from time to time. We know it occurs occasionally after a shunt, where the portal flow probably does reverse, and this even with an open shunt. In such patients the portal vein can be clamped and the portal pressure reading rechecked; in advanced cirrhosis with a patent portal vein at operation, the portal pressure usually does not rise after such obstruction.

I wonder if we should see the x-ray films at this time.

Dr. E. B. D. Neuhauser.—The film of the chest was essentially normal. The radiopaque dye flowed freely into the portal vein (Fig. 1). It appeared normally placed, and both the splenic and portal veins appeared patent.

Dr. Crane.—At least you do not see extra anastomotic channels all around the portal vein. I know that the making of these x-ray films is a little tricky. We have tried the method of using a plastic catheter with a No. 18 inside bore, particularly in two patients who had had a splenectomy. By picking up the top loop of jejunum and simply isolating a little vein at that level and directly passing in this small catheter, it can be tied in place and 70 per cent Urokon injected. By using a catheter instead of a needle, one can inject the dye more rapidly and securely.

I would think that this splenorenal shunt was indicated in such a patient with the prime prerequisite for operation, namely, bleeding esophageal varices. When esophageal varices are proved, but not bleeding, then indication for shunt is debatable. I would think that in childhood one would probably allow a 5- or 6-year-old child to grow as much as possible before subjecting her to a shunt, and, in general, feeling has been rather conservative, I gather, in patients who have nonbleeding varices. But again, Palmer and his associates,[3] at the Walter Reed Hospital, do not feel that way; they have begun doing shunts in their patients the minute they demonstrate varices in the pres-

ence of liver disease. In a recent paper of Palmer's,[4] seven adult patients with esophageal varices, but no bleeding, were brought into the hospital to have a shunt. Of those seven, three died after massive hemorrhage before a shunt could be performed. He quotes that as evidence for not waiting in this situation.

peritoneal cavity that thickens up the peritoneal coat, hardens, and makes the veins fibrotic and fragile.

This patient was not jaundiced, suggesting that she was not in terminal liver failure, and her liver function tests were stable. She was not on the downgrade at the time surgery

Fig. 1.—The radiopaque material injected in the splenic pulp is outlining the splenic and portal veins. Collateral vessels are seen in the lower abdomen and in the region of the cardia.

This girl had no ascites. Ascites has two adverse effects in the minds of one contemplating shunt surgery. First, it accompanies low protein values and indicates that the liver can stand less anesthesia, anoxia, bleeding, surgery, and stress. Second, it makes the operation a little harder, technically, in that there is something about a high protein fluid in the

was done. Many of our adult patients are rapidly failing when we first see them, because they come in with massive bleeding. Their first bleeding episode severely damages the liver because of the accompanying shock and anoxia.

What about the future of this patient? I think most people would agree that her liver function will not

be changed by the shunt. Presumably, her liver disease, whatever sort it is, will proceed pretty much the way it would otherwise. If she is going to be able to regenerate liver parenchyma and improve over the months, she probably will; and if she is going to go on and scar more severely, her prognosis, so far as the liver is concerned, will not be changed by the procedure. I am sure that this shunt is almost certainly open. Often the barium swallow will show diminution in the size of varices, and the larger the shunt the more likely it is that these varices will look smaller in a barium swallow. Yet, Dr. Palmer, who puts needles in these varices to measure the pressure, finds there is no firm correlation between the pressure in the vein and the appearance by x-ray.[4] The fact that she was 11 years old rather than 3 or 4, I think, would be in her favor, because the splenic vein would be larger. Also, she had a large spleen, so that the splenic vein is going to be larger than if she had a very small spleen; and the size of the shunt initially is of great importance. She had an excellent pressure differential across the shunt and this, too, is prognostically important.

DR. JOHN CRAIG.—Dr. Gross, would you like to say a word now?

DR. ROBERT GROSS.—I think Dr. Crane has covered this very well, and there are only small points that I would like to take up. First, I was a little horrified when I was told this case was to be presented, for, so far as I knew, all of our patients who have had splenorenal shunts are still alive. Fortunately, this patient is still among the living.

I think the indications for shunt were quite clear in this girl. In this hospital there has been a long interest in portal hypertension. In the years gone by, because of the writings of Dr. Smith and Dr. Howard,[5] when bleeding occurred in portal hypertension, we called it the Smith-Howard syndrome. The spleens of these children would go down in size, and when they recovered from bleeding the spleens would again increase in size. When these children start to bleed, mortality rates are high, and approximately half of them are dead within two or three years. You will find one who may bleed a few times in early childhood and then go along perfectly well for a long time. One who was in this hospital when he was 4 or 5 years old had several bad bouts of bleeding and then had no more until his early 20's, when he died of severe bleeding. In an individual case there may be great variation and one cannot give any reliable prognosis. When one is dealing with portal hypertension in adults the vast majority of subjects have portal hypertension as a result of hepatic obstruction. They have had hepatitis, cirrhosis, and blocking of the intrahepatic portal system. Conversely, in dealing with children one finds that there are a considerable number who, as Dr. Crane says, have had perfectly normal livers but have an extrahepatic block, usually due to some infection in the early months of life. So, in dealing with a childhood group, one has a little better material than in the adult years.

This shunt was done by Dr. Colin Ferguson, who was then the chief resident, and I think he did a superb job on it. He preferred to join the

splenic vein to the left renal vein. This was large enough to permit a very good anastomosis. We have done about a dozen of these. The over-all picture has been really quite good. We have been somewhat concerned about how small an individual we can perform such a shunt on, because as we deal with younger and younger patients, there is going to be a limit below which the vessels are not big enough to perform a shunt. A few years ago we performed one on a child 3 years of age; we got a good shunt but we felt that we were lucky. Last year we had one that was about 2½ years old, a child weighing 24 pounds. Again, we felt very lucky and thought that was probably the lower limit. Just a few days ago Dr. Nicholas Stahl operated upon a small baby weighing 13 pounds. I just did not believe it was going to be possible to do a shunt, but he did a superb job on it and brought the splenic vein and the renal vein together in a very nice way. But certainly there are going to be some of the smaller children where we will not have vessels big enough to make a shunt that is going to stay open. It has been established that there is a marked change in the over-all picture, at least in the six years that we have followed through postoperative cases here. None of them have died. There is one who bled some six months later, but we know that that was not an ideal shunt. Yet, she had only that one episode and has gone two years with no bleeding. So far as I know none of the other eleven patients have had any bleeding at any time and they are all alive, so that we are quite optimistic about it. That is particularly true if one is dealing with an individual whose primary problem is a block in the portal system outside the liver, as it is in a considerable number of our patients.

Is the shunt open or not? As you say, in this patient we think that the shunt is open because this youngster is getting on fairly well. There are various ways for determining whether or not these shunts are open. Dr. Crane mentioned one, and that is by direct puncture of the varices to see what their pressures are. I have not used that method because it is the kind of test one cannot repeat very often, and it requires a general anesthesia and then introduction under direct vision of a needle into a vein in the esophagus. There is a possibility of producing infection, and I am not too sure of the results obtained. Dr. Ben Isenman, in Denver, is studying this problem by feeding the patient various products which release ammonia. If the shunt is obstructed, the administered material must go through the liver; it is detoxified and one does not find a very high rise of ammonia in the peripheral circulating blood. Conversely, if the shunt is still open, administered material is passed directly into the peripheral circulation and the ammonia is at a higher level in the peripheral blood. So, in a rough way, one can tell whether or not the shunt is open. Dr. Getteling and his group in New York are instilling into the sigmoid a solution containing a radioactive substance that is absorbed by the descending colon. If the shunt is closed, all that blood must go up through the portal system and through the liver, and it takes a long time before it gets to the periphery. Its appearance in the peripheral circulation

can be determined by a Geiger counter placed over the arm. If the splenorenal shunt is open the material from the left side of the colon goes up the inferior mesenteric vein and is very quickly passed into the systemic peripheral circulation. I think it is going to develop as a useful test.

One point, finally, that I think ought to be mentioned is the effect of a shunt on existing hepatitis. So far as I know, the presence of a shunt, such as a splenorenal shunt, has no effect on the underlying liver disease. Dr. Gellis, I hope you will speak of this because I understand that you have had some feelings that maybe a shunt does have some curative value on the underlying liver disease. I wish you would either defend or deny it.

DR. CRAIG.—Dr. Gross, before you sit down I wonder if you would answer one question? Do you believe that sometimes a splenectomy alone is curative?

DR. GROSS.—Yes, I am sure it is. As one goes over the old records of fifteen or twenty years ago, there are occasional cases in which the only thing that was available was splenectomy. Occasionally the surgeon tried to perform an omentopexy by scarring the abdominal wall and gluing the omentum up to it in the hope that some shunts would establish, but I do not think they accomplished very much. In all cases the spleen was removed. That procedure certainly does reduce the amount of blood flowing into the portal system. About 20 per cent of the blood that goes into the portal system comes through the splenic artery and the spleen. In an occasional case, where there is only a moderate picture of portal hypertension, such a reduction in blood flow is just enough to turn the tide. Generally, it will not; but as we go back through our old records, we find a few of them in which removal of the spleen was enough to help them.

A PHYSICIAN.—What happens to the size of the spleen after the shunt?

DR. GROSS.—Well, you have to take a spleen out to do a shunt. You take the spleen out and then anastomose the end of the splenic vein to the left renal vein.

A PHYSICIAN.—In this case that Dr. Stahl did a few days ago, were the sutures interrupted all the way around or just anteriorly?

DR. GROSS.—That was a small baby, 13 pounds; and here you have the problem of what is going to happen in the next twenty years, if this patient lives. He now has a shunt which is only a few millimeters in diameter but when he gets along to a sizable individual he would like to have that opening bigger, and with that in mind the anastomosis was done with interrupted sutures, which gave it the best chance to grow a little bit.

DR. SYDNEY GELLIS.—I do not think there is any difference of opinion between us about what one might do for the liver, by a shunt. I think the slight difference of opinion arose over a case six years ago, the question being whether one should do a shunt in the face of positive liver function tests and evidence of liver dysfunction. We feel that in some cases, so far as the esophageal varices are concerned, the only hope is in a shunt and we are willing to take the chance

that we will get through the operation with a living patient at the end. In the case in question, you did a beautiful shunt on the patient, and she has never had any difficulty since. She has grown, and has gained remarkably. Surprisingly enough, and this is something I cannot explain at all, her positive liver function tests have come back to normal. That is the only evidence we might have, and it certainly is no evidence at all, that a shunt might do something for a damaged liver. We have been reviewing, with Dr. Craig, these patients with portal hypertension. I might just list off what has happened. I think it is especially interesting in view of what Dr. Gross has said about splenectomy alone as a possible help. I have now seen two children who had primary hypersplenism diagnosed by Dr. Louis Diamond, apparently secondary to something that went on at birth. Those children had splenectomies, both at about the age of 5 years, which relieved the primary hypersplenism. But they have since returned with esophageal varices with repeated bleeding episodes. Now there is no way of doing an easy shunt operation on them. So, on the basis of those two cases, I argued very strongly against surgical interference in primary hypersplenism, unless the situation is really a desperate one, and have pleaded for doing a shunt at that time instead of just straight splenectomy. But after going over these cases with Dr. Craig, I am not quite too sure of the ground. From the period 1925 to 1954,[6] nineteen cases of so-called primary portal hypertension were studied here. The age of onset varied from 1 to 9 years, hematemesis and tarry stools were the presenting symptoms in fourteen of the nineteen cases, and marked splenomegaly was present in the remaining ones. In one child the diagnosis of primary portal hypertension was established only when he was explored surgically, following trauma of the abdomen. All the patients were entirely well and free of symptoms prior to the onset of their bleeding or splenomegaly. It was interesting to note that seven of the nineteen children had a history of purulent infection and three others had severe respiratory infections and diarrhea during the newborn period. None of the children had ever been jaundiced. On physical examination they all showed marked splenomegaly, but only seven of them showed hepatomegaly, and there the enlargement was slight in all cases. Seven of the children showed ascites and seventeen had esophageal varices. Only nine in the latter group, however, had changes that could be definitely demonstrated by x-ray studies with barium. Many of the children showed signs of congestive splenomegaly, and in eight the total white count was below 4,000, in six the total platelet count was below 100,000; there was no depression of polymorphonuclears, however. Liver function tests were positive in two of the eleven patients studied, except for a slightly increased retention of Bromsulphalein in two others. The other laboratory studies were essentially negative. Three of the patients were treated by transfusion and watchful waiting. Two of these died from esophageal bleeding and the third from debilitation, all within a short time after the diagnosis was established. Eleven were

treated by splenectomy alone. Of these, two have been lost track of, and one died in the immediate postoperative period. Five of the remaining eight patients treated by splenectomy had recurrences of esophageal bleeding, sufficiently severe to cause death in two children, six months and one year after splenectomy. This occurred in two more patients, nine and ten years after splenectomy; but they were successfully treated by transfusion and are doing moderately well at the present time. In one patient, recurrences occurred regularly for the first ten years after splenectomy, but this gradually improved, so that at the present time she has had no further bleeding for a period of four years. She has otherwise been entirely well and leads a normal life. Her liver function tests have been repeatedly negative. Three of the children have had no recurrences of bleeding, one, one and one-half, and four years after splenectomy. However, we cannot be sure that recurrences may not occur in the immediate future. Five of the patients whom we have studied, who had splenorenal shunts, have been doing very well. They have now gone one and one-half, one and one-half, four, four and five years, respectively, after splenorenal shunts, and have had no recurrence of esophageal bleeding. That roughly summarizes the experience that we have had. I feel that if a child has esophageal varices we should not hold off on operation, even though we have evidence that the liver is damaged, because I would guess that the only hope lay in operating upon the child.

Dr. Craig.—The patient under discussion today had a very large spleen. It weighed 475 grams, ten times the normal size, and was minimally fibrotic. On the external surface there was a depressed area which was rather opaque and white, and I thought, up until this morning, that this might be an infarct; but since we have gone over another such spleen just today, I recognize that it is where the Diodrast was injected. It caused necrosis in large areas of the spleen. The sinusoids were prominent, with prominent sinusoidal lining cells. There was little increase in the amount of fibrosis. The Malpighian follicles were quite small. There were occasional peripenicillar lakes, that is, large areas of greatly dilated sinusoids which occasionally became thrombosed and fibrotic. The liver (Fig. 2) showed a fairly far-advanced cirrhosis. There was almost complete remodeling of the lobules, although in certain instances the lobular pattern was partially maintained. We have considered this an example of postnecrotic scarring with large lobules, irregular lobulation, and irregular regeneration of the lobules. There was a good deal of inflammation with large numbers of plasma cells and many lymphocytes. Some proliferation of the bile ducts was present. There was almost no fatty change. Among the nineteen cases Dr. Gellis mentioned, there were seven cases in which liver sections were obtained when the spleen was removed for portal hypertension. In two of these livers there was an inadequate cause for the hypertension.

So, in these two, one must assume that there was some difficulty outside the liver, giving rise to the hypertension and, supposedly, this was a block

in the portal vein. Among the five cases that came to autopsy having no cirrhosis, the diagnosis of portal vein obstruction was confirmed in all instances. As I mentioned before, the great majority of our cases of portal hypertension appear to be due to cirrhosis, arising secondary to hepatitis. In nine of thirty instances of cirrhosis signs of cirrhosis. Occasionally they had continuing evidence of liver damage. In twelve other cases the onset of the liver disease was insidious and was not related to a definite episode of jaundice. Most of these cases came into the hospital primarily with symptoms of ascites or obstruction, with esophageal varices,

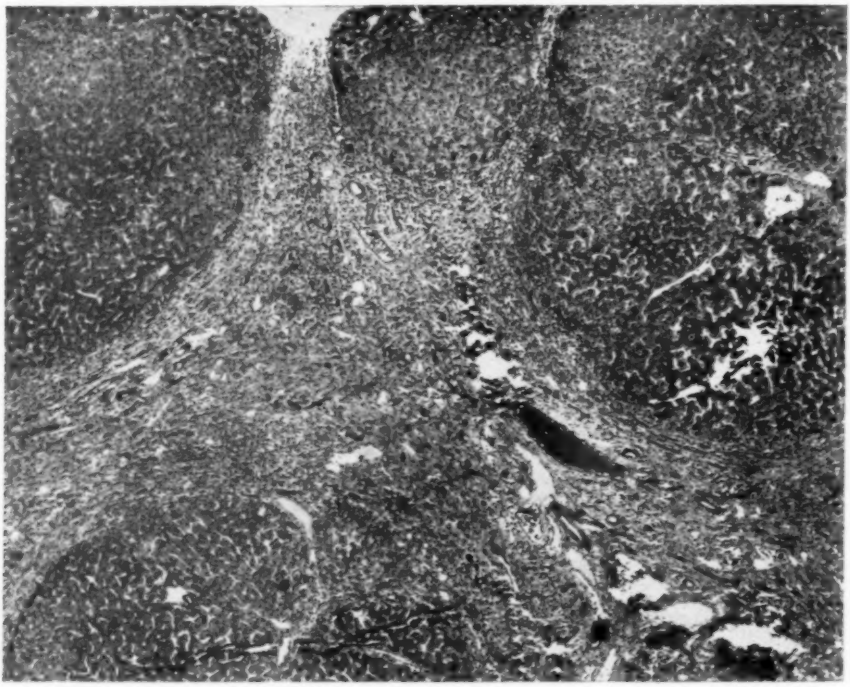

Fig. 2.—Liver. Marked lobular distortions and periportal fibrosis are seen. (Hematoxylin and eosin; ×85.)

that we have studied, it followed neonatal hepatitis in children who developed jaundice shortly after birth and remained jaundiced for long periods of time. Eight others had definite episodes of jaundice in childhood, with a sharp onset of illness. Then, after a period of recovery, they went on to develop the symptoms and as in the case under discussion today. In most of these cases of cirrhosis, which also had the picture of postnecrotic scarring, there were obstruction and enlargement of the spleen, yet there was comparatively little fibrosis in the spleen. In the two groups with postnecrotic scarring and cirrhosis,[7] the livers were all greatly

enlarged in contrast to those cases that began with neonatal hepatitis. Those livers were much smaller in comparison. So we believe, at least from our experience, that hepatitis seems to be a very important part in the causation of cirrhosis and portal hypertension in these children.

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Medical Progress

THE BACTERIAL FLORA OF THE INTESTINAL TRACT: CHANGES IN DIARRHEAL DISEASE AND FOLLOWING ANTIMICROBIAL THERAPY

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DIARRHEA remains one of the most common diseases with which pediatricians must deal. Its etiology has been attributed to practically every organism found in the stool, and viral agents have been suspected when only members of the so-called "normal flora" are isolated. Except when known enteric pathogens are recovered, it is difficult to know whether or not the presence of an organism has any causal significance. To definitely establish an etiological relationship, it would be necessary to show that: (1) the organism is present in predominant numbers in the stools of the majority of cases of a particular epidemic; (2) the organism is found rarely, if at all, in healthy individuals; (3) the time of suppression of the organism coincides with the onset of clinical improvement; (4) the presence of the organism in large numbers does not represent merely its overgrowth due to the suppression of other members of the flora by an unidentified agent; and (5) the host responds to the infection by the production of antibody. Unfortunately, such clear-cut evidence is not available in most cases.

Until the beginning of extensive use of antibiotics, the alterations in the gastrointestinal flora associated with clinical diarrhea were of primary interest. It is now apparent that extensive changes may be produced iatrogenically by the use of antimicrobial agents. These changes may or may not be associated with disease. This discussion will attempt to review two main questions: (1) the relationship of the "normal flora" to diarrheal disease, and (2) the relationship to diarrhea of the changes in the intestinal flora produced by antimicrobial agents.

NORMAL INTESTINAL BACTERIAL FLORA IN CHILDREN

The difference between the intestinal flora of the breast-fed and the artificially fed newborn infant is well established. Meconium is sterile, but in as little time as a few hours after birth it is possible to culture organisms from the rectum. These bacteria are inconsistent in type and few in number and depend on the particular bacterial environment in which the infant finds himself. The breast-fed infant develops a typical flora within a few days. Babero,[1] by

intubating both breast-fed and formula-fed infants was able to obtain cultures from various portions of the gastrointestinal tract. In the breast-fed group, the duodenum was relatively sterile. The flora of the jejunum consisted mainly of enterococci, especially *Sreptococcus bifidus*. These increased in number until they were found in large numbers in the upper ileum. There was marked bacterial proliferation in the cecum and distal to it, and small numbers of gram-negative organisms were recovered, *Escherichia coli* and *Aerobacter aerogenes* being the most common. Lactobacillus was never cultured above the terminal ileum, but accounted for about 90 per cent of the organisms found in the rectum. This organism is responsible for the gram-positive nature of the stool of the breast-fed newborn infant which has been noted by numerous observers.

The flora of the upper gastrointestinal tract of the formula-fed infants was very similar to that of the breast-fed group. Above the terminal ileum only enterococci were found. Gram-positive bacilli were grown from the gut distal to the terminal ileum, but they did not constitute such a large percentage of the stool and were also noted to present a varied morphology. In these infants, members of the coli-aerogenes group occurred at higher levels. Staphylococci and streptococci were present in both the small and the large intestines, and spore-formers, including *Clostridium welchii*, were also present in the latter. Stained smear of the stool is predominantly gram-negative.

These differences have been attributed to the nature and proportions of protein and carbohydrate in the diet, and it has been stated that artificial feedings with low protein and high carbohydrate will produce an intestinal flora similar to that of breast milk. In this study, however, those infants who received formulas with such characteristics did not have stools resembling bacteriologically those of the infants receiving breast milk. It has also been reported that it is the short-chained fatty acids (C8-C14) which inhibit both *Lactobacillus bifidus* and its mutant, *L. acidophilus*, leaving the coli-aerogenes group relatively unaffected. An "adapted" milk modified to largely eliminate these fatty acids was given to a second group of infants; their stools did show a higher percentage of gram-positive bacteria than did the stools of infants on other types of "adapted" milks. The exact significance of this difference in flora is not known; but it has long been observed that breast-fed infants are less susceptible to epidemic diarrhea of the newborn than are infants on other types of feedings.[2]

Control groups of various studies on gastroenteritis offer an additional source of information concerning the normal intestinal flora.[3-5] Proteus does not appear to be a natural inhabitant of the intestinal tract of normal breast-fed infants, but is occasionally found in the stools of healthy, artificially fed infants. In the latter group, when it exists in small numbers, it has no significance, with the possible exception of *P. morganii*. The relative proportion of Proteus to the coliforms is of more importance than their mere presence. The same general statements apply to the paracolons and Klebsiella. The "pathogenic" types of *Esch. coli* are not found in the stools of normal breast-fed infants, and only rarely in

healthy infants on cow's milk formulas.[6-9] Usually infants who do harbor the organism have been in contact with clinical cases of diarrhea attributed to this agent. Once the infant is established on feedings other than breast milk there is little change in flora during the remainder of infancy[10] and, indeed, the remainder of childhood.

It should be mentioned that under unusual circumstances, potential pathogens may be recovered from a large number of asymptomatic infants.[11]

INTESTINAL FLORA IN CHILDREN WITH GASTROENTERITIS

Except for members of the Salmonella and Shigella groups, there has been much controversy over the pathogenicity of the organisms cultured from the stools of children with diarrhea. There follows an attempt to summarize the evidence incriminating various members of the "normal flora" which have been isolated from children with gastroenteritis.

I. *Escherichia coli.*—Since methods have been developed to type by agglutination members of this group, three serotypes have appeared to have more than a chance relationship to diarrhea, especially in infancy: 0111B4, 055B5, and 0127B8. Other types have been incriminated, but these three are to date the most important.

Esch. coli has been regarded as a normal inhabitant of the gastrointestinal tract and its isolation from the stools of infants with diarrhea was given little attention until 1927, when Adam isolated a biochemically unique strain characterized by the fermentation of saccharose and rhamnose from the stools of infants with epidemic diarrhea.* A similar organism was recovered by Cziglany[6] in 1941 from an epidemic in Budapest. In 1947, the strains of *Esch. coli* were clearly classified by Kaufman,[12] according to their antigenic properties. Identification is based on the O, K, and H antigens which represent, respectively, the somatic, capsular or envelope, and flagellar antigens. This classification has greatly simplified typing, and the strain which has most consistently been incriminated is that with the 111 type of somatic antigen and the B4 variety of capsular antigen. Some investigators feel that the colony characteristics, particularly on sorbital agar media,[13] allow identification of this strain with a high degree of accuracy, but confirmation rests on agglutination with specific sera.

Evidence pointing to the pathogenicity of this serotype may be divided into three groups: (1) its isolation in almost pure culture from the stools of infants involved in epidemics of diarrhea from whom no known pathogens may be isolated, and the demonstration that it occurs with a significantly lower incidence in the stools of healthy infants; (2) demonstration that its overgrowth is not due to an unidentified viral agent; (3) demonstration, in the individuals involved, of a rising agglutinin titer; and (4) the production of gastroenteritis in previously healthy individuals by the oral administration of this organism, and the onset of symptoms and the recovery of the organism from the stools after the incubation period of the disease.

*Quoted by Giles.[5]

During the past fifteen years, there have been numerous reports of epidemic diarrhea associated with *Esch. coli* 0111B4.[6, 11-25] In these studies, this organism was isolated from the stools of clinical cases, and was found in almost pure culture in the majority. It was also isolated from the noses and throats of some of the babies. Only a small number of the healthy controls harbored this organism in the gastrointestinal or respiratory tracts.

Attempts to demonstrate a virus in addition to this serotype of *Esch coli* in the stools of involved infants have been consistently negative.[4, 6, 23, 26]

Relatively few workers have studied the sera of acutely ill and convalescent patients in an attempt to demonstrate a rising agglutinin titer. Several investigators have been able to show a significant increase in some patients.[6, 20, 21, 23, 27] In one study on premature infants with *Esch. coli* 0111B4 diarrhea, both the hemagglutination technique and the conventional agglutination techniques were utilized but a specific antibody response was not elicited. It was felt that this might be due to the poor antibody response associated with prematurity.[22]

The fourth approach in demonstrating pathogenicity lies in the production of disease in previously healthy subjects by the administration of the organism. In animal experimentation, diarrhea has been produced in baby guinea pigs but not in young mice, rabbits, or kittens by feeding *Esch. coli* 0111B4.[6] It has been possible to produce the disease by administering the organism orally to a 2-month-old hydrocephalic infant.[9] The onset of the diarrhea coincided with the appearance of this serotype in the nose, throat, and stools of the infant. A mild form of gastroenteritis can be produced by feeding this organism to adult volunteers,[11, 28] and Neter[9] was able to demonstrate the development of specific bacterial agglutinins and *Esch. coli* hemagglutinins in such subjects. Such an antibody response was not observed in controls who ingested nonpathogenic strains of *Esch. coli.*

The characteristic clinical picture of the diarrhea caused by this organism is that of a severe gastroenteritis in the young infant which develops after an incubation period ranging from two to eighteen days. The illness lasts one to two weeks and there are no clinical findings which differentiate it from other forms of severe infantile gastroenteritis. Artificially fed babies are more susceptible to this, as well as other infections, than are those on breast feedings. Few cases have occurred in children over 1 year of age. The mortality rate varies and has been as high as 44 per cent. Outbreaks are characterized by a high rate of cross-infection,[29, 30] and it has been demonstrated that the organism is present in the air of cubicles housing infected infants, and that it can survive in dust as long as twenty-seven days.[29] Asymptomatic carriers, most frequently either adult contacts or infants who have recovered from the disease, are an important factor in the prolongation of epidemics. Relapses following withdrawal of antibiotic therapy is also a problem, and is estimated to occur in 5 to 10 per cent of the cases.[13]

The isolation of *Esch. coli* 0111B4 from cases of sporadic diarrhea has

also been observed.[31, 32, 33] As in the epidemic form, there is nothing clinically which points to this serotype as the etiological agent. Young infants are most frequently involved, and they may harbor the organism in the respiratory as well as gastrointestinal tracts. Healthy infants examined simultaneously are found to harbor other *Esch. coli*, but not 0111B4.

A few writers question the pathogenicity of this serotype, because they have been able to isolate it from a significant number of healthy control infants.[31, 33] It should be mentioned, however, that in most cases the controls were infants who had been in contact with clinical cases. All that one can conclude from such evidence is that the organism can exist in the absence of disease.

The varied antibiotic sensitivities which have been encountered have contributed to the difficulty in clinical management, and it may be of interest to mention the experience with various therapeutic agents. The combination of penicillin and sulfa consistently has been disappointing.[17, 27, 35] Streptomycin, both orally and by the intramuscular route, has been of no value.[6, 15, 17, 35] The appearance of this serotype in the stools of children receiving these drugs has been reported, as well as their failure to produce clinical improvement.

Response to the broad-spectrum antibiotics has been variable. Chloromycetin has been shown to have a specific suppressive effect on *Esch. coli* 0111B4, leaving relatively unaffected the rest of the *Esch. coli* flora.[35] Despite its ability to reproduce initial improvement in some epidemics, however, the emergence of resistant organisms and the bacteriological and clinical relapse following its withdrawal limit its usefulness.[34, 36] It has been ineffective in the treatment of carriers,[34] and its administration prophylactically has not prevented the spread of an outbreak, at least in the epidemic reported by Wheeler.[21] Its prophylactic use in one epidemic in England was associated with a marked decrease in cross-infection.[35]

In vitro studies indicate a sensitivity to Aureomycin and Terramycin in most cases,[37, 38] and slow, gradual loss of sensitivity is characteristic. Clinical results have shown the drugs to be moderately useful. Magnussen[17] reports good results with Aureomycin. He gave this drug orally to eight infants who had both positive stool and nose and/or throat cultures. Cultures were clear in an average of three days and clinical improvement was definite. Other workers have considered it a useful drug in this infection but Stulberg[22] found no clinical or bacteriological response with its use. Terramycin was used by Carrie,[38] and he felt that it is without effect in controlling diarrhea or preventing relapse. Neter[18] found it useful in the small group of patients which he studied.

Neomycin is the most promising agent at present. It is considered the drug of choice by Wheeler[21] who found it as useful as Chloromycetin in improving the clinical picture, and superior to it in that there was no problem of emergence of resistant strains. The treatment of all patients and adult contact carriers resulted in a prompt halt of the epidemic. Stulberg[22] also reports good results with this drug, although some of his patients did have bacteriological relapses. Because these infants had in the meantime been exposed to new

cases and because they responded well to a second course of neomycin, it was not established that resistant organisms were responsible. Neomycin-resistant organisms have been reported.

Reports in the literature concerning *Esch. coli* 055B5 are much fewer than those describing *Esch. coli* 0111B4, but its association with epidemics of diarrhea seems definite. As with 0111B4, identification is based on agglutination techniques, and there is little cross agglutination between these two types.

Evidence concerning its pathogenicity rests mainly on its association with epidemics of diarrhea,[6, 7, 16, 24, 25, 36] and the fact that it is rarely found in babies without gastroenteritis. In a group of controls, Giles[6] was unable to recover this serotype from the stools of breast-fed infants or any large number of those who were receiving cow's milk feedings. Most of the patients are under one year of age. Additional evidence for the pathogenicity of this serotype lies in the finding that ingestion of this type by adult volunteers[39] also produces clinical gastroenteritis, which does not result when other serotypes are used. The development of group-specific *Esch. coli* agglutinins and bacterial hemagglutinins after the ingestion of *Esch. coli* 055B5 has also been demonstrated in one adult.

Cooper[40] reported an outbreak of gastroenteritis in which *Esch. coli* 127B8 appeared to be the causative organism. Of forty-four infants from whom this serotype was isolated, forty-three had gastroenteritis, and it was recovered in one of eighty-two adult contacts. It is interesting that over one-half of the positive cultures were obtained while patients were on various antibiotics. Neomycin produced the most satisfactory results therapeutically, but was not completely reliable in eradicating the organism from the stool. Other writers[36, 41] agree that infants under the age of 3 months comprise the group usually affected. Even when children over this age group are in close contact with affected infants, they rarely develop a positive stool culture.

The measurement of serum agglutinins has been only sporadically successful, probably because of the evanescent character of the antibody.

II. *Paracolons.*—Proving the pathogenicity of these organisms involves the same problems encountered in attempting to prove pathogenicity of any member of the "normal flora." The fact that several authors have shown a rise in antibody titer,[5, 42] as well as the mere presence of these organisms in patients with diarrhea, indicates that at least in certain instances their role is not that of saprophytes.

Although these organisms are found normally in small numbers in stools of older infants, their presence does not constitute a normal finding in very young infants. Epidemics of gastroenteritis associated with the recovery of paracolons from the stool have been recorded by several observers.[3, 42-45] It has also been possible to demonstrate a significant antibody response in the individuals involved which cannot be demonstrated in control subjects, but it has also been shown that the presence of such agglutinins may represent a cross-reaction to the Salmonella and Shigella groups.[5] The exact role of the paracolons in diarrheal disease is far

from established. Paracolon bacilli may be only saprophytes, since they have frequently been found in the stools of healthy individuals. They may represent harmless agents in patients with diarrhea. They may be associated with known pathogens and play a secondary role as irritants in diarrheal disease; or they may be the primary cause of diarrhea in susceptible individuals, especially infants.[44]

Two factors must be considered in evaluating the meaning of the recovery of this group of agents from the stools of infants with diarrhea. The absolute number does not appear to be as important as the ratio of the number of paracolons to the number of coliforms. Certain strains appear to have a greater potential for pathogenicity: Arizona, Bethesda, 29911, and Melbourne.

III. *Proteus.*—This group of organisms holds a place comparable to that of the paracolons as etiological agents in diarrhea. As mentioned previously, Proteus is not a natural inhabitant of the intestinal tract of normal breast-fed infants, but is occasionally found in the stools of healthy artificially fed babies. This group of organisms has been mentioned as the predominant organism in the stools of infantile diarrhea by several investigators.[3, 47, 48] *P. morganii* has been incriminated more often than other species, but does not appear to be the only possible pathogen in the group. Both *P. vulgaris*[47] and *P. mirabilis*[48] have epidemics of diarrhea attributed to their presence.

Attempts to demonstrate the presence of agglutinins in the sera of patients with gastroenteritis from whom either *P. morganii* or *P. vulgaris* was isolated have been disappointing, but this is not taken as proof against their pathogenicity, since it has been observed that a patient with proved *P. vulgaris* peritonitis did not show an antigenic response.[44] Neter[47] postulates that this may be due to the dissociation of the organism within the intestinal tract. This premise is based on his demonstration in an infant that the feeding of a strain of *P. vulgaris* led to the appearance of the organism in the stools, but that the antigenic structure differed from the strain fed, although the two were identical biochemically. Lack of antigenic activity has been noted by others, and it is felt that this may account for the chronic recurrent type of infection which is usually seen.

IV. *Pseudomonas.*—Diarrhea in which this organism has been recovered as the predominating organism may present the picture of a protracted mild diarrhea,[55, 58] or a rapidly progressive disease with a significant mortality. It is not always possible to blame the disease on the overgrowth of this organism secondary to antibiotic therapy.[50-54]

Although it has been shown that agglutinins may be demonstrated in the sera of convalescent patients, this is of little value in establishing pathogenicity because it has been noted that a nonspecific rise in titer may be found in patients who have other types of infections.[52]

V. *Staphylococcus aureus.*—A number of workers have reported the association of this organism with infantile diarrhea,[55-58] but the evidence for its pathogenicity is largely, if not entirely, circumstantial. That hemolytic *Staph. aureus* is present in the stool of asymptomatic infants has been noted frequently.[59-61] It does not occur as a predominant organism,

however. It is usually thought to be nonpathogenic, but in one study the same strain which appeared as a harmless saprophyte in the majority of the infants was also cultured from the site of pathology in an infant with a breast abscess, three with conjunctivitis, one with pyoderma, and six with infantile diarrhea.[62]

VI. *Streptococci.*—Little mention has been made of the possible etiological significance of this organism in gastroenteritis in the literature of the past fifteen years, and it has been noted that there is no difference in their incidence in the stools of normal children and those suffering from gastroenteritis. Gale,[63] however, did report "large numbers of beta hemolytic Group D streptococci" as a "feature" of stools in certain outbreaks of neonatal diarrhea. These organisms are characterized by a high tyrosine decarboxylase activity and the power to establish themselves in the fecal flora of the infant rat, or man, "properties not possessed by normal enterococci." The author reports the production of diarrhea in infant rats by feeding these organisms, and states that the symptoms are most marked "when the diet was such as to render the intestinal medium optimal for the action of tyrosine carboxylase."

VII. *Other Organisms.*—Klebsiella has been mentioned by several authors as the probable causative organism in outbreaks of infantile diarrhea.[64-66] Sternberg[66] reports a pair of premature twins who developed diarrhea on the first day of life; in one, this was associated with stomatitis. The Klebsiella organism isolated had the same antigenic structure as that found by Walcher[64] in a small group of patients with diarrhea, most of whom were less than 1 year of age. Worfel[65] describes two epidemics of diarrhea of the newborn in which Klebsiella was isolated from the stools of the affected infants. One of the infants who excreted the organism developed an agglutination titer to the organism of 1:256.

Bacillus faecalis alcaligenes and *Aerobacter aerogenes* have also been mentioned as possible pathogens, but evidence is scanty.

CHANGES IN THE INTESTINAL FLORA FOLLOWING ANTIBIOTIC THERAPY

It became obvious shortly after antibiotics began to be used extensively that serious side effects could follow even relatively short periods of therapy. Changes in the respiratory and gastrointestinal flora constitute an important complication of chemo- and antibiotic therapy, for they may result in disease.[67-72] The alteration in flora may represent the overgrowth of an organism which developed resistance to the antibiotic during its administration, or overgrowth by organisms naturally resistant to the drug. This disturbance of the normal flora by an overgrowth of resistant bacteria or fungi is one important cause of antibiotic diarrhea. A second type is that in which no organism can be cultured, the antibiotic having completely eliminated all bacteria.

Two main sources of information concerning antibiotic-produced changes in the gastrointestinal flora are the studies concerning the possible benefit of these agents in sterilizing the gut by their use prior to gastrointestinal surgery; and studies of the changes in flora resulting from

the use of antibiotic agents prophylactically or in the treatment of a specific infection. In reviewing the information available, the effects of specific antibiotics on intestinal flora will be discussed first, and, second, mention will be made of two gastrointestinal complications which have shown themselves deserving of attention: staphylococcal enteritis, and overgrowth by *Candida albicans*.

Of the sulfa drugs, only the insoluble group produce any appreciable effect. Sulfasuxidine and Sulfathalidine have been found useful in the preoperative management of patients being prepared for gastrointestinal surgery, because they produce a significant reduction in the coliform count.[70-72] After a brief period of administration, some decrease in enterococci, pseudomonas, and proteus may be expected. Continued administration of the drug usually results in a stable bacteriological picture, but there is some tendency for a gradual return to normal, and withdrawal of the drug produces a prompt return to normal.

As would be expected, penicillin does not have a significant suppressive action on the gram-negative flora of the gut. It has been shown by Thomas,[73] however, that there are significant differences in the degree of resistance of these organisms, so that massive doses of the drug might be expected to produce a significant alteration. He found that the gram-negative bacilli fall into the following order of decreasing susceptibility to penicillin: salmonella, proteus, shigella, escherichia, aerobacter. There is also evidence that bizarre involutional forms may be produced in the presence of inhibitory but not bacteriostatic concentrations of penicillin.

Administration of oral penicillin as a prophylactic measure has not been found to have significant effect on the gastrointestinal flora.[74] *Streptococcus faecalis* is somewhat inhibited. This is in contrast to the throat, where the normal flora is primarily gram-positive. In this case, there is frequently an emergence of a gram-negative flora, but in Lipman's[74] study, this was not associated with the production of disease, and emergence of resistant gram-positive organisms was not a problem. Return to a pretreatment flora took from one week to three months.

The action of streptomycin on the intestinal flora is characterized by an initial reduction in the gram-negative flora, but resistant organisms emerge rapidly, and overwhelming infection by such an organism has been reported.[75-80]

Aureomycin has proved to be a potent agent in the elimination of the normal flora of the gastrointestinal tract and also in the production of serious side effects. It has been found to rapidly suppress *Esch. coli*, Aerobacter, *Str. faecalis*, and anaerobic sporeformers. There is, however, a frequent increase in proteus, pseudomonas, and yeasts, and occasionally staphylococci.[67, 72, 81-85]

Terramycin, as well as Aureomycin, has been most frequently implicated in the production of *Staph. enteritis*. The occurrence of diarrhea following the use of Terramycin is one of its well-known side effects, and the simultaneous appearance of a predominance of *Staph. aureus* in the stool has been reported by a number of workers.

Administration of this drug produces changes in the intestinal flora very similar to those found following the use of Aureomycin. The normal flora is supplanted by staphylococci, yeasts, and paracolons, as well as proteus. There may be resistant coliforms found which emerge during treatment.[72, 85, 86]

Chloromycetin produces a reduction in the coliform flora, but no marked qualitative changes in the fecal bacterial forms. There is less suppression of both the coliforms and the enterococci than results from the use of Aureomycin or Terramycin, but its prolonged use may result in the overgrowth of resistant organisms, most frequently yeasts and pseudomonas,[67, 72, 84]

The effects of tetracycline on the gastrointestinal flora have been studied by Metzger.[87] Enterococci were not found to be affected, but coliforms were reduced and *Staph. aureus* was increased, as were yeasts.[87]

Neomycin has been found to be a potent agent in its ability to suppress the coliform group and, less consistently, pseudomonas and enterococci. Emergence of resistant organisms has not been commonly observed.[88]

Two complications which are serious and have been found to follow the use of antibiotics, which are pertinent to a discussion of changes in the normal gastrointestinal flora, are the production of *Staph. enteritis,* and the overgrowth by yeasts and fungi, especially *Candida albicans.* Most of the detailed reports in the literature describe these complications in adults but they both appear in children.

Staph. enteritis must be differentiated from pseudomembranous enterocolitis. Both present the clinical picture of diarrhea often resulting in shock, and *Staph. aureus* is usually recovered from the stool. The latter, however, has been reported prior to the advent of antibiotics and chiefly follows bowel surgery. It has not been possible to correlate the pathological lesion specifically with antibiotic therapy. *Staph. enteritis* has been a complication primarily of Terramycin administration, but has also been reported in patients who had received Aureomycin, penicillin, and dihydrostreptomycin.[89, 92] The organisms recovered in the stool are usually resistant to penicillin and the majority show no sensitivity to Terramycin or Aureomycin. Coliforms are present in very small numbers or not at all. Strains of similar resistance patterns may be found in the throats of the patients. It is postulated that this entity results either from a suppression of the normal flora which allows for overgrowth of staphylococci or the introduction of a virulent strain of staphylococcus. Another suggestion is that there may be a direct stimulation of staphylococci under the influence of antibiotics. Good clinical response has been the rule when patients with this complication are treated early with erythromycin, but one can expect some increase in the number of organisms resistant to this agent.

Fungal infection complicating antibiotic therapy may involve a single system, or may present as a systemic infection. In the latter situation, the picture is grave and fatality not unusual. Such secondary fungal infections have been rare with the parenteral use of penicillin and streptomycin, but oral moniliasis, although it was well known before antibiotics were used extensively, has followed the administration of penicillin by

mouth. The introduction of the "oral" antibiotics has more frequently been associated with monilial infections, and these have been noted to be associated often with signs suggestive of vitamin B deficiency.[93, 94]

Woods'[93] study of moniliasis in a group of twenty-five patients covered an age range of 1 to 70 years. Twenty had *C. albicans* cultured from the oropharynx, and the drugs which had been administered before this finding included Chloromycetin, penicillin parenterally and as lozenges, Aureomycin capsules and lozenges, Terramycin capsules, streptomycin parenterally, and numerous combinations of the above. Three patients presented the picture of mild persistent diarrhea. One had received a prolonged course of intramuscular penicillin, the second had been on intramuscular penicillin and Aureomycin; the third had received only oral Aureomycin. Candida grew abundantly in the stool. The author offers a number of postulates as possible explanations for fungal overgrowth: (1) a direct stimulating effect of the growth of Candida by antibiotics; (2) the suppression of competing organisms; (3) a change in the pH of the environment through an alteration in the bacterial flora; (4) a change in the host tissue resistance as a result of a vitamin deficiency of some other physiopathological change.

It has been stated that Aureomycin has a direct stimulatory effect on the growth of *C. albicans*. Moore[95] studied the action of a dilute Aureomycin preparation and of Aureomycin crystals on colonies of the fungus, and reported that the former caused the cells closely associated with the drug to form giant forms, and that the cells at some distance but in contact with the diluted Aureomycin produced small, but rapidly dividing forms. This work has not been confirmed, and other investigators express the opinion that a direct stimulatory effect by any of the antibiotics is not likely.[93, 96, 97] The possible role in a change in pH as an etiological factor in the overgrowth by Candida does not seem likely, since it is possible to grow it well in media with a wide pH range. So far, the evidence points toward the elimination of competing organisms as the most plausible explanation.

Antibiotic diarrhea, therefore, frequently involves members of the normal flora which have been found to be potentially pathogenic, in this case, because their resistance pattern enables them to escape after broad-spectrum drugs are used. This may be a point of evidence in favor of the view that these organisms produce disease only after the host has been altered in some manner which favors their growth. Such general factors as debilitation and dehydration have been mentioned, but we are becoming increasingly aware of the importance of alteration in the host by these potent drugs. It is also evident that marked changes in the gastrointestinal flora are not always accompanied by disease.

SUMMARY

1. The stool of the breast-fed infant is characterized by a high percentage of gram-positive organisms, most prominently *L. bifidus*. That of the artificially fed infant is more complex, and there is a prominence of the coli-aerogenes group. Staphylococci

and streptococci and a few spore-formers are present. The diet, rather than the age, determines the intestinal flora. There is little change in the flora from that of the artificially fed baby to that of the older child. Except in breast-fed infants, most strains of proteus and paracolons may be considered normal inhabitants if they are present in small numbers.

2. The three serotypes of *Esch. coli* that have most frequently been considered pathogenic in the production of infantile gastroenteritis are 0111B4, 055B5, and 0127B8. Evidence pointing to the pathogenicity of these types includes the isolation of the organism from infants with diarrhea and the demonstration of clinical improvement coincident with its elimination from the stool cultures; the demonstration that it rarely occurs in asymptomatic individuals, unless they have been in contact with positive cases; failure to demonstrate a virus in the stools of such infants; the demonstration of a rise in antibody response during convalescence; and production of disease by the administration of the organism to susceptible individuals. Clinically, epidemics in which these organisms are involved are characterized by a severe illness with a substantial mortality rate and a high degree of contagiousness. Therapy is complicated by resistance of the organisms to many of the antibiotics. Although strains isolated from various epidemics vary in their sensitivities, neomycin at present is the most promising agent.

3. Other members of the "normal flora" of the gastrointestinal tract which have been considered pathogenic in gastroenteritis include paracolons (particularly strains of the Arizona, Bethesda, 29911, and Melbourne groups), proteus (especially morganii), pseudomonas, *Staph. aureus*, streptococcus, and Klebsiella. Proof of pathogenicity is difficult because any of these organisms may be found in the stools of healthy individuals; their presence even in increased numbers in patients with diarrhea does not establish an etiological relationship; ability to produce an antigenic response in the host, even in the presence of overwhelming infection, cannot always be demonstrated. Evidence largely favors the hypothesis that any of these groups may represent pathogens in the infant group which is unusually susceptible.

4. Administration of practically all antibiotics produces some change in the gastrointestinal flora. The rapid suppression of the gram-negative organisms following the use of Aureomycin or Terramycin has most commonly resulted in the serious complication of *Staph. enteritis*. The broad-spectrum drugs are also most commonly incriminated in the overgrowth by potentially dangerous and frequently resistant organisms, such as yeasts, pseudomonas, and proteus, and *Candida albicans*.

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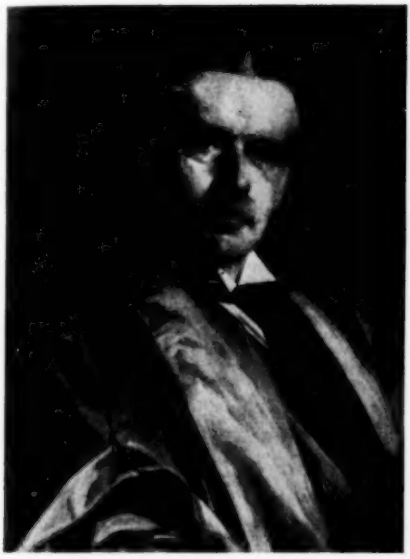
Pediatric Profiles

George Frederic Still

(1868-1941)



From the painting in the Royal Academy, 1935, by Gerald Kelly, R.A.

THE way of a pioneer is usually hard, perhaps because of the unknown terrain, perhaps because it may involve a cleavage from the customs and mode of thought of one's fellow men. In the country of his birth Still was the first doctor to confine his professional life to the study and care of children, and while this entitles him to be regarded as the founder of English pediatrics, it meant for several years a stern struggle for a livelihood. Fourteen years were to elapse after his entry into the competitive market of consulting medicine before he felt free to take a holiday. In the first of these years his income from professional practice would have purchased, at today's values, one television licence, to which in the next year he might have added a dozen gallons of petrol, and in the third year a couple of pounds of tobacco. Yet the time was to come when he would have to put up both hands to fend off the pressure of private practice, and it must have been this experience which led him to give such shrewd advice to a junior colleague who, on starting private practice, had asked whether it was necessary to lease expensive consulting rooms. The answer was, "Take a cheap room in a back street, for when you are young no one will want to consult you, and as you get older they will seek you out wherever you are."

A man must be made of sterling material to pass unscathed through the fires of hardship. Although Still had been born in what in modern jargon would be called an underprivileged suburb of London, he was of Cornish extraction, as was betokened in his speech by the burr of his R's, and he possessed all the dour independence, the religious scruples, the honesty of purpose, and the high principles which, while by no means confined to the Cornishman, certainly are to be looked for in that corner of England. He was a keeper of the Sabbath. So long as his mother lived the

two could be seen on Sunday mornings walking to church, she on his arm, and he in his frock coat carrying his hymnal. Much later he became a dry-fly fisherman, and would invite friends for the week end to his stretch of river in Hampshire, where they might fish to their hearts' content on Saturday, but not on Sunday. Were there, however, a child dangerously ill in his ward at King's College Hospital, the week end in the country was cheerfully discarded, and Still would visit the child on Sunday, making the journey in a jolting tramcar, for he did not drive himself, and the Sabbath was to be a day of rest for his chauffeur. As a very low speed limit was imposed on the chauffeur, it may be surmised that other days in the week were also relatively restful for him.

On leaving school, Still went to Cambridge University, where at Caius College his study of medicine was deferred until he had taken a first in classics, and thereafter for the remainder of his life he could always obtain solace and relaxation from the hurly-burly of the twentieth century by reading original Latin and Greek. Toward the end of his professional career an evening visitor to his home would be very likely to find Still in his drawing room sitting upright on a hard chair, while surrounded by soft easy chairs, with one leg crossed over the other and a book of classical poems on his knee. It is not therefore surprising that he was able to compose the Latin verses to "Carmen Scholae Medicinae," the song of King's College Hospital Medical School.

The reader will probably be prepared by now for the information that Still was a bachelor. He was certainly shy of women; on one occasion, faced with the imminent prospect of an introduction to a junior colleague's wife, he sought escape down a side corridor. Sometimes it seemed that he suffered mothers for the sake of the children, for he seldom had a good word for them, and in his private practice could treat them in the brusque manner they probably deserved. In his last illness, no nurse stayed the course for more than two or three days, and on one occasion his medical attendant was locked out. Yet his ward sisters were devoted to him. The fact remains that Still was courteous, ready to listen, and only sharp with his tongue if a child would benefit. Sometimes made irascible by fatigue, he was never known to lose his temper, and his patience was never better seen than when he had to act as a chairman of committee, a task he accepted only because it was his duty. It was difficult to expose his sense of humor, for he was never known to tell a funny story, and certainly no one ever had the temerity to risk trying one on him.

Physically Still was a small man, thin and wiry, but of quite striking appearance, with a well-proportioned head, iron-gray hair parted in the center, a trim gray mustache, rather bushy eyebrows, and deep-set eyes latterly ringed with xanthelasma palpebrarum. His voice carried well, his speech was clear and firm, he was never at a loss for a word, and would occasionally make use of quotations to illustrate a point. A black suit with striped trousers, a white shirt, and black silk tie was his invariable London attire.

To attend a teaching ward round was indeed a lesson for the student.

The children, except those severely ill, were already undressed and wrapped in a blanket or shawl. The case history having been read by the student, Still would then examine the child, which was the great moment. Percussion of the chest was both rapid and light, followed by such a darting of the stethoscope from place to place that the student soon realized it was only necessary to hear one respiratory exchange per area in order to learn all that the stethoscope could teach. The knee jerks were elicited by a tap of the fingers, the ophthalmoscope was often in evidence, the abdomen and throat were examined, the student held up the test tubes showing the results of urinalysis, and a surprisingly complete examination was made in a matter of minutes, the child meanwhile playing with the great man's watch. As a concluding item a trolley was wheeled forward, on which under a thick glass plate was ready for inspection a sample of the stool from each infant. A discourse followed, lasting from some five to ten minutes, and the class then moved on to the next cot.

No one could watch Still at work without quickly realizing that here was a man who, apart from a deep knowledge of children's ailments, had a genuine and most profound love for them, and an almost uncanny understanding of their point of view. The students and nurses round the cot might well be the recipients of a fierce glance or a merited rebuke from the Chief, but the child, with her hand in his, drew from him courage, companionship, and peace. In his book *The Silver Fleece,* Collis, who was one of Still's house physicians, gives an account of him visiting an ill and fretful child in hospital, passing his hand under the bedclothes to examine the abdomen, and then sending for a surgical colleague. In order that the latter might have the same chance of a satisfactory examination, Still nursed the child in his arms, whereupon his diagnosis of pneumococcal peritonitis was accepted. On another occasion the outlook for a child ill with septic peritonitis was in question; Still sat by the cotside for many minutes, feeling the pulse and watching the child as a cat watches a mouse, until at last came the assurance "she will get well." Many a time one has seen him, when others had failed, speedily reduce a fractious child to contentment, and his greatest joy was, on the occasion of a special visit to hospital, to dispense with the services of his house physician and ward sister, and be left alone with the children. Yet he intensely disliked trying to teach against a background of noise, and a child, rowdy for no good reason, would find himself, during a teaching ward round, banished to the bathroom. A child did not have to be ill to receive Still's affection; on his week-end visits to Hampshire he was usually to be seen escorted from the station by the children of the village, each vying to hold his hand.

The infliction of pain or apprehension on a child seemed to hurt Still more than the patient. He would never wear a white coat in the wards in case it might send a shiver of alarm through a child. If his house physician was required to needle a chest, Still would be up on his toes, drawing in his breath with anxiety, and as likely as not would grasp the intern's arm at the critical

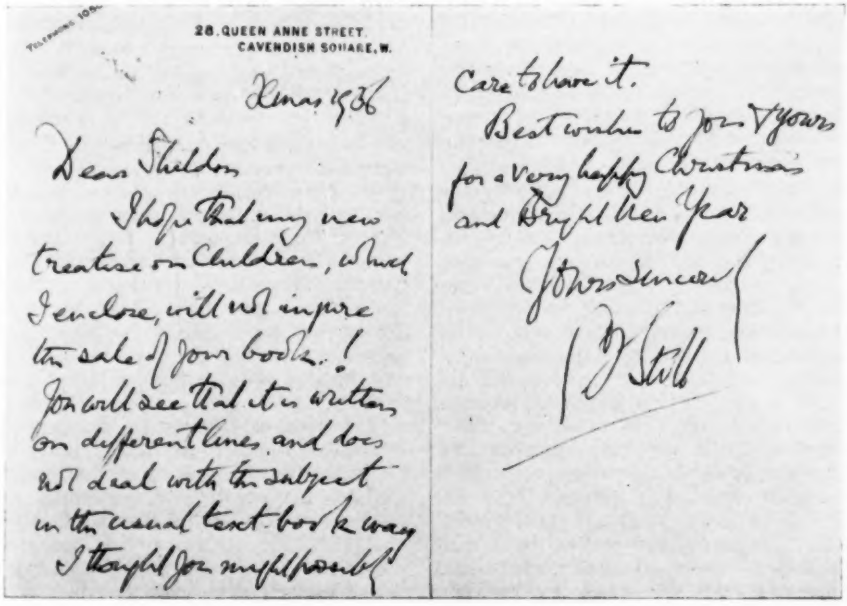
moment. In the early days of hypertrophic pyloric stenosis, he, with his surgical colleague Mr. Burghard, had a run of successes with Loreta's operation such as no other team could emulate, but the scene in the theater beggared description, with Burghard roaring like a lion from start to finish, a matter of seldom more than ten minutes, and Still twittering with fear lest something should go wrong. It was a merciful thing that Still lived when he did, and so never had to witness the treatment of tuberculous meningitis by daily intrathecal injections; certainly he would have been in the forefront of trying antibiotics by oral administration. His were the days of careful prescribing and of what might now seem like an almost pathetic faith in the power of drugs. Dosage was for him a very precise matter, and it was no uncommon thing for his house physician's dose of, say, chloral hydrate to be abruptly curtailed by a fraction of a grain or cautiously increased. Mixtures for children had also to be rendered palatable as his house physician soon realized after being made to taste some of his own brews.

Still must have been one of the most meticulous of men, and long preparation went into anything of his making. Ex tempore speaking was not to his liking. His popular and beautifully written textbook on *Common Disorders and Diseases of Children* was written and rewritten several times before its polish was high enough for its author to allow it to appear in print. The evening before a teaching ward round his house physician had to telephone Dr. Still to tell him what new cases were in the ward so that the subject matter could be prepared and the statistical accompaniments be correct. Still always maintained a complete index, fully cross-referenced, of all his cases from both hospital and private practice, and was therefore in the happy position of being able, at short notice, to quote from his own figures in support of his experience. Any of his registrars, who prepared an article for publication under Still's guidance, had to be equally meticulous. The article when written would be taken to Still, and then evening after evening the two would pore over each sentence, first of all reducing it to good English, then recasting it until the sentence truly expressed the author's view, and finally another review to protect the reader from any possible misinterpretation.

It remains to weave into this backcloth something of Still's career. Qualifying from Guy's Hospital, he soon became a house physician at The Hospital for Sick Children, Great Ormond Street, and continued to serve that remarkable institution as registrar and later as physician for over thirty years, giving to the hospital all he had, and taking from it all that it could give. He had as colleagues men of great talent, but as was fitting, he never spoke of them in front of a junior, although he often expressed his admiration for his friend Dr. John Thomson, the father of Scottish pediatrics. It was during his period as registrar that in 1897 he described the disease of joints, associated with enlargement of glands and spleen that was to become known by his name, and in the following year discovered the organism of posterior basic meningitis and identified it with the organism previously described by Weichselbaum as the cause of cerebrospinal meningitis. A year

later King's College Hospital decided to found a children's department, the first undergraduate hospital in London to do so, and invited Still to be its first physician. In 1906 King's College, London, created the honorary post of Professor of Children's Diseases to which Still was elected.

Untrammeled by family responsibilities, and prepared to work for children even when tired out, there flowed from him during the next thirty years a glittering stream of original articles, informed contributions to other men's textbooks, memorial lectures, and so forth, sandwiched with increasing difficulty into the ever-growing demands of a public thirsting for his knowledge and skill. He was honored by Their Royal Highnesses The Duke and Duchess of York, later to become King George VI and Queen Elizabeth, who entrusted to him the health of their two daughters, and for this personal service to his Sovereign, Still was in 1937 created K.C.V.O. Among other honors he was President of the Third International Paediatric Congress in London in 1933, and was the first President of the British Paediatric Association. For many years he was Chairman of the National Association for the Prevention of Infant Mortality.


28 QUEEN ANNE STREET
CAVENDISH SQUARE, W.

Xmas 1936

Dear Sheldon

I hope that my new treatise on Children, which I enclose, will not injure the sale of your books! You will see that it is written on different lines and does not deal with the subject in the usual text-book way

I thought you might possibly care to have it.

Best wishes to you & yours for a very happy Christmas and Bright New Year

John Spencer Still

In addition to his textbook, other book publications included *The History of Paediatrics* (1931) in which the subject is traced from Hippocrates to the end of the eighteenth century; *Common Happenings in Childhood* (1938); a book of charming verses entitled *Concerning Children and Other Things* (1936). The photograph showing Still's handwriting is taken from his letter that accompanied a presentation copy of these poems.

Wilfrid Sheldon

Comments on Current Literature

CARDIAC INVOLVEMENT IN CERTAIN VIRUS DISEASES

INVOLVEMENT of the heart as an accompanying feature of virus disease has been recognized clinically for many years, the occurrence of myocarditis being accepted as a possibility in such virus diseases as poliomyelitis, measles, mumps, infectious mononucleosis, viral pneumonias, and in various encephalitides.

The February (1956) issue of the *American Journal of Medical Sciences* carries a report by Saphir and his associates[1] at the Michael Reese Hospital, in which are reviewed the clinical records and necropsy findings of four patients who died of acute viral hepatitis (infectious) with acute myocarditis. One of the four was a child of 6 years. Three of these patients succumbed after a relatively short course of the infection; two showed electrocardiographic changes which were interpreted in retrospect as evidence of myocarditis. Pathologically the changes in the myocardium consisted of "minute foci of necrosis and a more diffuse serous inflammation. In three of the four cases the bundle of His was involved with necrosis of isolated fibers, hemorrhage and an acute inflammatory exudate."[1] Hepatic findings in these patients at autopsy were characteristic of acute viral hepatitis.

In the case of the 6-year-old child, both the clinical findings and the autopsy studies are of special interest. The clinical course from onset of symptoms to fatal outcome was relatively short, about twenty days, including five days of hospitalization. In this child the typical liver changes usually associated with acute viral hepatitis were found, and a severe myocarditis. Prominent changes were observed in the left bundle branch. Microscopically the most characteristic feature of the myocarditis was the presence of "minute foci of necrosis of isolated muscle bundles. These were often surrounded by lymphocytes, myocardial reticulocytes and a few polymorphonuclear leukocytes."[1] Minute isolated necrotic muscle fibers were also present around which inflammatory cells were not seen; isolated muscle-fiber necrosis in the bundle of His was noted. No attempts at virus isolation were made, and as the authors point out, proof that the myocarditis observed in these patients with typical viral hepatitis was caused by the same agent as the hepatitis is lacking. Nevertheless, these associated findings are of interest, especially in patients whose clinical course was short, and since the type of focal necrosis of the myocardium which was found in all four cases, has been reported in other fatal cases of virus disease of which myocarditis was considered to be a feature.

Myocarditis in several newborn infants has been reported recently, associated with an outbreak of Coxsackie group B virus infection in a maternity hospital in Johannesburg, South Africa. This detailed study from the Transvaal Memorial Hospital for Children appeared in THE JOURNAL OF PEDIATRICS for January, 1956.[2] Bornholm disease was prevalent in Johannesburg at the time. The ten infants included in this report ranged in age

from 5 to 17 days; some of the infants became ill during the hospital stay of the mother, and some soon after discharge to the home. These infants "characteristically showed a biphasic type of illness, the initial episode consisting of a few loose stools followed after an interval of three to eight days by a fulminating illness ending in circulatory collapse. Of the ten babies affected, six died."[2] Marked tachycardia was noted, and the electrocardiographic tracing showed abnormal T_1 wave. Post-mortem examinations carried out in three of the fatal cases revealed a "patchy myocarditis" as the outstanding heart finding. In one of the three, a focus of encephalitis was observed. Death appeared to be due to acute heart failure and general circulatory collapse.

Laboratory studies and bacteriologic investigations failed to yield pertinent information. However, by mouse inoculation, Coxsackie group B virus was isolated from brain tissue of two fatal cases, and from fecal specimens of two infants who recovered. The strains of virus were identified as belonging to Coxsackie group B, and one strain, followed somewhat longer in serial passage in mice, was classified further as group B, type 3. Subsequently a strain of group B Coxsackie virus was isolated from the heart muscle of an infant nine days of age who died soon after admission to the Transvaal Hospital. The symptoms and signs of myocarditis in this infant were similar to those in the other cases, and autopsy findings were likewise consistent. It seemed significant that one mother discharged from the maternity division developed soon after discharge a biphasic illness characterized in the second phase by meningoencephalitis. Unfortunately no investigative work was carried out in this instance.

A recent experimental investigation employing Coxsackie virus of group B, type 3, concerns the induction of myocardial lesions in adult mice by this strain of Coxsackie virus plus cortisone. This report by Kilbourne, Wilson and Perrier[3] appears in the April (1956) issue of the *Journal of Clinical Investigation*. Coxsackie viruses are characterized by their virulence for suckling or very young mice and hamsters, and by their "inability to induce manifest disease in adults of these species."[3] This resistance of adult experimental animals has been one of the problems in the study of Coxsackie strains and their isolation from clinical cases. Group B Coxsackie strains multiply to some extent in adult mice, producing a nonfatal disease largely involving the pancreas.[4] In connection with earlier work, Kilbourne, Horsfall, and others[5] found that "the administration of cortisone to the adult mouse changes this state of intrinsic resistance to one of marked susceptibility resulting in death,"[3] and that the administration of cortisone allows a prolonged viremia and persistence of virus in the lungs and brain. This cortisone effect has been noted only with those strains of Coxsackie (group B) which seem to be able to multiply to some extent in adult mice in the absence of cortisone. For practical purposes efforts were made by Kilbourne and his group to adapt a strain of this type to the adult mouse by serial passage in the cortisone-treated host.[3, 6] The virus employed was recovered directly in cortisone-treated adult mice from the stool of a patient with epidemic pleurodynia, without intervening passage in infant mice. In these adult mice gross necrotic lesions of the myocardium were observed, the nature and pathogenesis of which are described in the recent report. Control studies indicated that in infant mice paralyzed by Coxsackie strains the myocardial lesions which accompany skeletal muscle paralysis are not a prominent feature of the infection, and that similar minor myocardial changes do occur in inoculated adult mice (group B strains), in the absence of any apparent illness. Gross disseminated myocardial necrosis may be induced "by the injection of cortisone into the adult mouse infected with a Coxsackie virus intrinsically capable of multiplication

in the myocardium."[3] Administration separately of virus or cortisone resulted in minimal and inconstant focal necrosis, and microscopic study of inoculated controls indicated that "in the absence of exogenous cortisone, virus may multiply to a high concentration in the myocardium without inducing microscopically apparent pathologic change. Multiplication of the virus is not manifestly influenced by cortisone,"[3] indicating that the effect observed is the result of altered host response, rather than of increased virus titer. A very interesting aspect of this work in experimental animals was that the gross myocardial necrosis resulting from the infection of Coxsackie virus and cortisone could be prevented by the simultaneous administration of type specific viral antiserum.

These authors, aware of the reports of fatal myocarditis in human infants, and those on encephalomyocarditis which have appeared in recent years, state that the experimentally "demonstrated cardiotropicity of B-3 virus is of more than academic interest . . . ," and that "it is not unreasonable to speculate on the possible conversion of the benign pleurodynia of (human) adults to more serious, if not fatal, disease by the stimulus of endogenous or exogenous corticosteroids."[3] Even in those virus infections which are considered mild under ordinary circumstances, the danger of complications, or of possible widespread dissemination of virus in the body, needs to be re-emphasized, especially in view of the general use of the corticosteroids in therapy.

RUSSELL J. BLATTNER

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News and Notes

At the annual meeting of the **Society for Pediatric Research** held at Buck Hill Falls, May 8, 1956, the following officers were elected for 1956-1957:

President, Dr. William Wallace, Cleveland
Vice-President, Dr. Harry A. Waisman, Madison
Secretary-Treasurer, Dr. Sydney S. Gellis, Boston

The following candidates were elected for membership: Dr. Guilio Barbero, Philadelphia; Dr. Thomas Boggs, Philadelphia; Dr. Robert M. Chanock, Cincinnati; Dr. Marvin Cornblath, Baltimore; Dr. Joaquin Cravioto, Mexico City; Dr. J. Frederick Eagle, Buffalo; Dr. Heinz J. Eichenwald, New York; Dr. Silvester Frenk, Mexico City; Dr. Ruth Gross, San Francisco; Dr. Melvin Grumbach, New York; Dr. Albert Hennessy, Ann Arbor; Dr. Gerald Kerrigan, Boston; Dr. Sidney Kibrick, Boston; Dr. Lula Lubchenco, Denver; Dr. Robert McAllister, Philadelphia; Dr. Claude J. Migeon, Baltimore; Dr. C. Arden Miller, Kansas City; Dr. Richard Rowe, Toronto; Dr. Julius Rutzky, Detroit; Dr. Richard T. Smith, Minneapolis; Dr. Robert A. Ulstrom, Los Angeles.

The **George Henry Poncher Foundation** has been established in memory of the late Dr. Poncher with funds contributed by nearly two hundred of his friends. The purpose of the foundation is to make loans up to $1,000 available to premedical students at Valparaiso University and to medical students at the University of Illinois. The Fund will be administered by a representative of the University of Illinois Medical School, a representative of the community (Valparaiso), and a representative of Valparaiso University. The first committee under this arrangement consists of Dr. Edward F. Lis, Judge Burns of the Porter Circuit Court, and Mr. A. F. Scribner of Valparaiso University.

The **New York Medical College and Flower and Fifth Avenue Hospitals** announces a post-graduate course in *pediatric allergy* under the direction of Dr. Bret Ratner, Nov. 7, 1956, to May 29, 1957, thirty sessions, Wednesday, 9 A.M. to 4 P.M. Applicants must be certified in pediatrics or have the requirements for certification. Enrollment limited. Apply to Office of the Dean, New York Medical College, Fifth Avenue at 106th Street, New York 29, N. Y.

Books

Hunterdon Medical Center. Ray E. Trussell, M.D., Cambridge, Mass., 1956, Harvard University Press, 236 pages. Price $3.75.

The Rochester Regional Hospital Council. Leonard S. Rosenfeld, M.D., and Henry B. Makover, M.D., Cambridge, Mass., 1956, Harvard University Press, 204 pages. Price $3.50.

These two volumes, published for the Commonwealth Fund, are discussions of two of the recent experiments in providing better medical care on a regional basis.

The first describes an unusual rural "grass-root" community effort on a country-wide basis. Hunterdon is a county in western New Jersey with 38,000 inhabitants at the time the idea was born. It is 435 square miles in size and contains a number of small communities. Previous to the establishment of the Center, there was no hospital in the county, and medical service was provided by thirty-two general practitioners scattered throughout the various communities, but of whom only nineteen were active. For hospitalization, or specialist service, it was necessary to travel to one of the larger surrounding communities. The book presents in a narrative form the events, developments, and changing concepts that took place between the time the idea was proposed in a rather vague way by the Hunterdon Board of Agriculture in 1946 until the Center was opened in July, 1953, and the administrative and organizational problems that were encountered in the first two years of its functioning. The original concept of a hospital

was expanded to include facilities for health and preventive medicine. In 1949 an affiliation was made between the project and the Regional Hospital Plan of the New York University-Bellevue Medical Center which provides the house staff and guides the medical service. Of particular interest is the discussion of the medical problems that developed, and the working out of the relationships between the six full-time salaried specialists and the nineteen general practitioners who form the medical staff. As might be expected, many problems developed, and the spirit of understanding with which they have been studied and worked out reflects the work and attitude of Dr. Trussell, the director during the five crucial years while the Center was being established and put into operation. One gathers that nearly everyone involved in the Center is happy.

Considerable space is given to the pediatric department and its unusually liberal visiting policy for parents which was necessary because of the type of community served. The discussion of the experience of using parents in the care of hospitalized children will be of particular interest to the pediatric group. The book is unusually well written, and the reviewer found it of so much interest that it was read through in the course of twenty-four hours. We recommend it as one of the most interesting descriptions and discussions of a medical-social experiment that has appeared.

The volume discussing the Rochester Regional Hospital Council, in which the late Albert Kaiser was so active, will in comparison be found rather tedious reading except for those interested in similar projects. This is due to the fact that it is a study made by the Department of Administrative Medicine, Columbia University School of Public Health, for the Commonwealth Fund which has been supporting the project. Thus it is purely an objective, impartial survey of the accomplishments and failures of the Council. Of necessity, the text contains many statistics, as the Council was interested in a number of regional services as, for example, education, nursing, and cooperative purchasing.

B. S. V.

Pedatric Nursing. ed. 3. Gladys S. Benz, R.N., M.A., St. Louis, 1956, The C. V. Mosby Co., 634 pages. Price $5.25.

Benz's *Pediatric Nursing*, first published in 1948, has become a standard text in the field. It approaches the subject from the broad aspect of growth and development, as well as covering the nursing techniques involved in caring for the infant and sick child.

Neurology and Psychiatry in Childhood. Proceedings of the Association for Research in Nervous and Mental Disease, Baltimore, 1956, Williams & Wilkins Co., 504 pages.

These proceedings of the meeting held in December, 1954, contain a number of articles of unusual interest to the pediatrician. Some are much larger and more detailed than the account actually presented at the meeting. For example, the discussion of "The Cerebral Atrophies and Encephalomalacias of Infancy and Childhood" by Wolf and Cowen of Columbia is actually a monograph of 132 pages. The program was varied and wide in scope. Thus Caffey discusses the radiological feature of traumatic lesions in the growing skull, while the last part is a symposium on juvenile schizophrenia in which Kanner, Hirschberg and Bryant, and Bender presented formal reports, and we find Jensen, Szurek, Bradley, Allen, Crothers, Levy, and others participating in the discussion. In all, twenty-two formal discussions are printed and nearly all are related to the field of pediatrics. The discussion of infections of the central nervous system consisted of four papers by Alexander, Platou, Salt, and Hodes. Perhaps the unusual emphasis on pediatric aspects was due to McIntosh being president and on the program committee. The proceedings are well edited and printed, and deserve a wide reading as many of the topics are of unusual interest.

Herzkrankheiten im Säuglingsalter. E. Rossi, Leipzig, 1956, Georg Thieme.

The author presents his own clinical experience together with the recent literature and a clear and precise discussion of the various kinds of congenital heart disease covering the physiopathology, clinical picture, roentgen appearance, electrocardiographic findings, angiocardiography, catheterization, and therapy. Excellent photographs and tables enhance the text. This is a good textbook for the student and pediatrician.

BENJAMIN ZWIREN

Editor's Column

SUMMER READING

IT IS not unusual for publishers and periodicals to make their summer issues somewhat lighter in tone. It goes back to an attempt to cater to the now almost extinct "hammock trade." Obviously, such a course is impossible for scientific journals, but we thought some of our readers might enjoy sharing the amusement of the Editor when he recently had occasion to look over Volume 31 of *The Medical Record* of 1887, a journal published weekly in New York and one of the best of that era. For this reason we reprint a number of excerpts for this summer month's column. Undoubtedly the papers, editorial comments, and opinions published in the medical journals of today will be as amusing to physicians in the year A.D. 2025.

THE RELATIVE SMARTNESS OF DOCTORS' CHILDREN.—Galton has pointed out some very curious facts concerning the children of professional men. He found, from a study of the heredity of the members of some of the largest scientific societies of London, that the legal profession presented the most eminent men and the fewest idiots. The medical profession came next; and lastly clergymen, who produced the smallest number of eminent men and the largest number of idiots and feebleminded. The lawyers gave origin to six times as many more eminent men as the clergy. The clergy gave origin to six times as many more idiots and feebleminded as the lawyers.

SINGULAR MORTALITY AMONG MISS HOYT'S MEDICAL EXPERTS IN THE FAMOUS JESSE HOYT WILL CASE.—Since Miss Mary Hoyt commenced the contest, in 1883, against the probate of her father's will, five of her medical experts have been placed *hors de combat* by death, and one by insanity. . . . The medical witnesses and experts on the side of the executors are all alive.

SUICIDE AND PLUMBING.—A citizen in St. Louis committed suicide because compelled by the city health department to make proper connections from his house with the sewer.

THE DOCTOR'S HORSE.—A Correspondent asks us to furnish some general advice regarding the purchase of a horse for the country practitioner. . . .

We confess that the doctor's horse is something that seems at first a little outside of the regular lines of scientific inquiry. It will be at once admitted, however, that this noble animal forms a very important item in actual medical practice . . . since next to his professional education the doctor's horse is the most essential thing for his getting along. What avails the transcendent skill of Dr. A while Mrs. B lies in the throes of a crossed presentation ten miles away, and no horse? At such times the text-books on obstetrics give place beside the Arab steed which each good physician thinks he possesses. And as the mud-splashed gig lightly skims the earth, with the doctor over the seat, and ergot and ether under it, one knows that the doctor's horse is better than a medical course, for it is a medical courser. But the horse in question is not always a pleasure or a help. Balzac once said that, "It was more necessary for the doctor to have a carriage than to cure his patients," a bit of irony in which there is truth enough to cause much pain. The young man who is just beginning to make some progress thinks that he must buy a horse and carriage, to keep up appearances of continued prosperity, and the new establishment keeps him poorer than ever.

. . . It is a great many years since Pascal observed that, "If physicians did

not have their cassocks and their mules, they would not have duped the world, which cannot resist this show!" . . .

Perhaps our correspondent, who seems to be mainly anxious to know how he can get a three hundred dollar horse for fifty dollars, will be disappointed in getting only a homily like the foregoing. We will give him, however, a few practical hints, or, as such things are now in vogue, some "Don'ts" for the Doctor's Horse. Don't, for example, buy a white horse, for that is the color of Death's; and don't buy a black horse, for that is the color of the devil. . . . If you are a young man, with bills to pay, don't buy any horse at all.

[In a subsequent issue "Country Doctor" wrote the Editor, giving 12 "Dont's" of which a few are quoted.]

Having practiced more or less successfully in a Western State, emigrating from New England twelve years since, and always in a country district where a good horse, in the eyes of the public, is a better recommendation to favor than a diploma and a hospital course, may I add a few "dont's" to yours for the aid of the young doctor, who, of course, is the one who needs them.

1. Don't buy a horse till you have an office and a fair library, and can buy for cash; and then only when you need one.

5. Don't drive for "show." You will be found out if you do. Nor drive fast around town or elsewhere, unless necessary.

7. Don't swop horses and be known as a jockey.

8. Don't think more of your horse than you do of your patient, nor so much of your patient that you will kill your horse.

12. Don't buy a *horse* at all; buy a mare, for various reasons not necessary here to mention.

AN ENTERPRISING FEMALE CHARLATAN.—The *Pacific Record* states that a female doctor in San Diego, Cal., started a cancer epidemic, and her rooms were filled with patients, from each of whom she extracted a cancer "without pain," and was rapidly getting rich, until someone discovered that the "cancers" were pig-kidneys. Many female doctors have ridden this hobby of curing cancers into a good practice, without one atom of knowledge. It is only necessary to employ two or three women to declare that *they* have been cured, and the thing is done.

A DUEL TALKED OF.—We learn with pain that a personal altercation has occurred between Dr. Love and Dr. Todd, of St. Louis. Dr. Love, having editorially criticised Dr. Todd some time ago, was snubbed by the latter, who in turn was immediately struck by the former. These interchanges of opinion were then suspended temporarily, but a resumption of hostilities is talked of. Dr. Love is President of the Mississippi Valley Medical Association, and highly esteemed as a physician, besides being a stalwart advocate of the American Code of Ethics.

(Editor's Note: Dr. Love was a founder member of the American Pediatric Society.)

WOMEN AND THEIR ODORS.—Hysterical women under sexual or other excitement exhale an agreeable odor, say several eminent neurologists. A French writer goes further and says that in early youth many women exhale a perfume whose entrancement extends even to the clothes they have cast aside for the wash. Again, "in general hospitals one is never deceived, the female wards smell of butylic acid." With all due respect to distinguished experts in olfaction, it appears necessary to say that the foregoing is more or less preposterous nonsense. Female wards do not smell of butylic acid, and the perfume which extends to the clothes that have been given to the wash is more liable to be perspiratory, axillary, and leucorrhoeic than an entrancing emanation from Araby the Blest. Those who have observed an agreeable odor in women under sexual excitement are liable to the accusation of suffering from subjective disturbances at the time.

THE ETHICS OF ADVERTISING.—A correspondent from Kansas City informs us that he has read in the daily papers an account of another wonderful operation performed by a member of the staff of one of the teaching institutions in this city. Having seen similar reports of operations by the same individual, he very naturally inquires if it is necessary to belong to that

particular body of instructors in order to be allowed to advertise. In the West, he says, they are more refined and cultured in their methods than they are here. Physicians there bring themselves before the public in many ways, it is true, but in a manner more pleasing to their wished-for patrons. They pose as founders of societies of microscopy and art, are prominent in religious circles, and are foremost in all public enterprises and philanthropic schemes of every kind and sort.

This is all very true, and our correspondent is right in claiming that the Western methods are more refined and more in keeping with the requirements of the Code. But he fails to recognize the broad distinction between local and national advertising. The man who works what the wicked call the Sunday-school racket has only a limited sphere of usefulness. He may be called on to treat the clergyman of the parish gratuitously, and through him may get a few fees out of the members of the congregation. But the man who reports his marvellous operations, or who announces himself as delivering a course of lectures, in the papers throughout the country has a more lofty ambition. He desires to relieve the sufferings of his fellow-men everywhere, and not merely those residing within the limits of a narrow section. That our Western brethren are beginning to grasp this idea is evidenced by some startling tales in the papers of a dead person brought to life by a Chicago physician. That is more than the professor, with all his operations, has ever done.

INTUBATION OF THE LARYNX.—Dr. A. Jacobi, of New York, said that he felt obliged and was willing and anxious to discard the opinion he entertained two years ago and which he published in "Pepper's System of Medicine," with reference to intubation of the larynx, and wished to say that if anyone deserved credit for his discovery and his painstaking labor, it certainly was Dr. O'Dwyer. There was no doubt that a large number of children had been relieved immediately, not only temporarily, but permanently.

COUNT TOLSTOI ON PHYSICIANS.—Count Tolstoi may be a great novelist and a remarkable thinker, but if he never thought anything more original than the following, which is going the rounds of an admiring press, he should give up an unfruitful habit of systematic ratiocination. He says:

"This is where the strength of the physician lies, be he a quack, a homoeopath, or an allopath. He supplies the perennial demand for comfort, the craving for sympathy that every human sufferer feels, and of which the germs exist in the child. See a baby that has given itself a blow; it runs to its mother or its nurse to be kissed and have "the place" rubbed; and it actually suffers less for the pity and the caress. Why? Because it feels that they are bigger and wiser than itself, and have it in their power to help it. So the doctors were of a certain use to Natacha when they assured her that she would be better after taking the pills and the powders from the shop in Arbatskaia, which were put up in a neat little box, costing one ruble and seventy kopecks, and were to be dissolved in boiling water, and taken every two hours."

We do not know what was the matter with Natacha, but if it was constipation, or a real hard stomach-ache, for example, we would put blue pills and paregoric against a sense of the personal bigness of the doctor every time.

MORE ABOUT SPECIALISTS.—The latest contribution to the ethics of specialism is the article by Dr. Morris H. Henry in the last issue of the *North American Review*. . . .

Dr. Henry maintains that only those men are entitled to be called specialists, in the true sense of the term, who have laid a foundation by, at least, ten years of general practice, and who have eliminated from their practice all but a certain class of cases, in which they find themselves especially interested, and in the handling of which they have acquired a special tact. The relation of any and every part of the human body to the organic whole is so subtile that one must understand the whole in order thoroughly to understand a part. . . .

We shall have specialists as long as the world lasts. They have secured a position from which they cannot be dislodged. To

them is due the increase in positive knowledge in many departments of medical research. Specialists, however, are, contrary to what obtains in the case of poets, made and not born. This making can result only from general experience, and the subsequent narrowing of one's field of work.

MATERNITY HOSPITALS THAT NEED REFORMING.—If Dr. Herst's statistics, published in the *Medical News*, are correct, there is need of a very radical change in the methods followed by obstetricians and lay managers connected with some of our large maternity hospitals. For example, the death-rate from all causes in five hospitals, according to Herst, in 1885 was:

Louisville, City Hospital
3.75 per cent of all women confined.
Indianapolis, City Hospital
4.71 " " " " " "
King's County Hospital, L. I.
4.76 " " " " " "
Brooklyn Maternity
4.44 " " " " " "
New Orleans, Charity Hospital
10.22(!) " " " " " "

"This last record," adds the doctor, "reminds one of the days when Semmelweiss was struggling for reform in the Vienna Hospital, or when Tarnier first took charge of the Maternité."

CERTIFICATES OF ILLNESS.—We learn from the *Boston Medical and Surgical Journal* that the Faculty of Harvard College has promulgated the extrordinary rule that in all cases in which the college has heretofore required a physician's certificate to the fact of illness of absent students, such certificate must specify the cause of illness, in order that the Faculty may be able to judge of the validity of the excuse for absence. The *Journal* says that such a requirement is unjust to the physician and student. No doubt this is true, yet we fear that such a regulation would never have been made if Boston and Cambridge physicians had not got into lax habits in the matter of giving certificates.

BOXING THE EARS.—Nearly all blows upon the side of the head may injure the ear, and thus range themselves under this category. The custom of ear-boxing is of long standing; thus, according to ancient writers, the classical boxer regarded the ear as the most vulnerable part for the infliction of a blow with the deadly cestus. But, later on, early Christianity aimed a blow against this pagan custom, and with unflinching fortitude the non-combatant, when smitten upon one cheek, meekly presented the other to the still persistent advocate of corporal punishment. And it is due to this kindly example that custom no longer sanctions the practice, though the principle upon which it was founded may have been almost forgotten.

But a great amount of heedless and brutal punishment is still inflicted in this way, not only by pugilists and contestants generally, but also by teachers, parents, and others who find that a punch about the ears is generally a painful and most effectual means of chastisement.

[Editor's Note: Introductory paragraph to a paper by Samuel Sexton, M.D., of New York.]

DISABLED GREAT MEN.—The Emperor William is suffering from advanced senility, the Crown Prince from a laryngeal papilloma, and Bismarck from rheumatism; Mr. Gladstone has catarrhal troubles of his respiratory organs; Sir Michael Hicks-Beach has cataracts; Mr. Parnell has some unknown malady which makes him an invalid; Lord Randolph Churchill married an American lady and has the American disease, neurasthenia; Mr. Blaine is reported to be a *brightique;* Mr. Manning is hemiplegic; President Cleveland is rheumatic and lipomatosic; the Emperor of Russia is suffering from mental depression; Mr. Jacob Sharp is reported to be diabetic; while Father McGlynn and Mr. Editor O'Brien are not so well as they should be.

ANTE-MORTEM EARTH TREATMENT.—A distinguished Philadelphia Surgeon advocates the systematic use of earth as a topical application to wounds. This is a very old treatment, but heretofore surgeons have waited until after the patient was dead before making topical application of earth.

A SEVERE REMEDY FOR A MILD AFFECTION.—In a recent number of the

Gazette des Hôpitaux, Dr. Bertillon relates how he cured a child of the habit of sucking his thumb. He placed the boy on a chair, and, forcing him to look intently at a bright object, induced hypnotism. Then he suggested to the child that he ought not to suck his thumb, repeating the injunction three or four times. On being awakened, the boy complained of a feeling of weight in the head. The next day he refrained from sucking his thumbs, but resumed the habit a few days later. Then he was again hypnotized, and Dr. Bertillon commanded him sternly never to suck his thumbs again. The habit was not resumed after this, and the cure was pronounced complete.

We have cited this case merely as an illustration of a tendency, which is altogether too prevalent at the present time, to employ heroic remedies carelessly and without warrant, simply because of their novelty, when other and well-tried methods will answer every purpose. . . .

URTICARIA FROM COW'S MILK.—Dr. S. S. Cartwright writes that Dr. S. W. Reed, of Margaretville, N. Y., has a little patient, seven years old, in whom the use of cow's milk always produces an eruption of urticaria. Some four or five years ago he ordered milk for her, and, though told of the idiosyncrasy, insisted that she should take it. She did so, and was soon covered with an eruption of urticaria. A few days ago he ordered a poultice of bread and milk for a swelling on the child's neck, and in less than two hours an eruption of urticaria covered the neck and entire side of the face.

THE DECLINE OF AMERICAN MEDICINE.—Our young contemporary, the *Medical Standard*, writes in a very Stygian mood as regards the present condition of American medicine.

The fee-bills, it says, of most medical societies of the second decade of the present century are practically identical with those of the medical societies of the present time. American medical remuneration is now much less, proportionately, than it ever has been. With this decrease in pecuniary reward has come an almost equal decrease in social recognition. The physician no longer towers above the community as a member of that famous aristocratic triumvirate of the first three decades of the present century—the "parson," the "squire," and the "doctor." The "squire" has risen in prominence, but the "doctor" has fallen. Furthermore, we are told that there are no such towering giants as in the old days of Rush, and Mott, and McDowell. The scientific status of American medicine is also lower; and, in fine, we are all going to the bad. The explanation of all this is stated with a candor and precision characteristic of a great commercial centre instinct with true business feeling. It is because we as a profession have indulged too much in "humanitarian cant" and "canting pseudo-philanthropy," and have not kept pace with the business feeling and business methods of the age. The remedy, if we understand our contemporary correctly, is to give up philanthropy, or rather, pseudo-philanthropy, and conduct all professional affairs on business principles, or, to be more euphemistic, be guided by the principles of an advanced political economy.

TWENTY YEARS IN PRISON FOR BLOWING UP A PHYSICIAN.—The Maine method of dealing with doctors who are out when a patient calls is described by the *Lewiston Journal* as follows: "A physician in Monson went out of town when a certain person's child was sick. The child died; the father thereupon blew up the doctor's office with dynamite, saying that he did it for revenge—claiming that if the doctor 'had staid at home and attended to his business' his child would have lived. The doctor is sufficiently 'blown up' for his sins, but to have his office blown up is carrying things beyond physiological limits. The Maine dynamiter was sent to prison for twenty years."

A PSEUDO-MEDICAL CHARITY.—Against the protests of the profession, the Presbyterian Hospital [New York] has put up a dispensary building for out-patients in the midst of one of the wealthiest sections of the city. Such a building in such a place is utterly uncalled for.

INTERESTING TO SPORTSMEN.—Professor Parvin states that pruritus vulvae may be sometimes due to wild hairs.

STATES' RIGHTS AND HOSPITAL INTERNES.—A most extraordinary restriction has been established by the Legislature of Louisiana, according to *The Southwestern Medical Gazette*. The eminent body of local patriots in question voted $90,000 to Charity Hospital, "provided that only Louisianians should be permitted to compete for positions on the staff of the hospital!"

LONG BEARDS, "SANITAS," AND HIS COAT-TAILS.—

To the Editor of the Medical Record

Sir: "Sanitas" pictures the method of catching diphtheria, or the contagion, by bringing the whiskers, rather than coat-tails, near the patient's face when making a professional examination; and also says most doctors expose their faces by this manoeuvre rather than their coat-tails; but some may have idiosyncrasies which may destroy his argument. This is really very cunning, but let us see how it will work if applied to other cases. Diphtheria is not the only disease, nor is examining a patient the only method of getting a load of contagion which may be conveyed by the doctor. I have mentioned that contagious material may be deposited upon door-latches, car-seats, privy-seats, church pews, drinking-utensils, cash, clothing, or most any other substance. Now, I do not know what are the idiosyncrasies of some folks, but out West a man is not so likely to get contagion in his whiskers from car-seats, privy-seats, etc., as he is in his coat-tails. Verily, if "Sanitas" cuts off his whiskers as a measure of sanitary engineering, he must, if he carries out his good intentions, be found standing on his head in many places to save his coat-tails. . . .

BERI-BERI IN NEW YORK.—Several cases of beri-beri have been observed recently in New York. They were brought to the city on a vessel from San Francisco, nearly all the crew being attacked with the disease, and several dying. Most of the survivors were in a crippled state, and three were taken to Bellevue Hospital, where two died. Unfortunately the disease was not recognized at first, and no examination of the nerves, or the blood, and no culture-experiments were made. . . .

Drs. Cornelissen and Sugenoya, the one a Danish, the other a Japanese physician, living in Java, have shown that the micro-organism which causes beri-beri is very similar to the anthrax-bacillus. It is colored with fuchsin or gentian violet, and easily seen. It is found in the blood, muscles, nerves, and serous fluids.

THE COMING TREATMENT FOR PHTHISIS.—The treatment of phthisis by medicated gaseous enemata, devised by Dr. Bergeon, of Lyons, has recently received the attention and measured approbation of Dr. J. Henry Bennett, who gives a full account of it in the *British Medical Journal* of December 18, 1886. We have already explained the general principles of Bergeon's method. He found that carbonic acid gas introduced into the system by the veins of the intestines was harmless, painless, and without special medical effect; in other words, it was a practically inert gas. He then medicated this with sulphuretted hydrogen, and the medicated gas was injected per rectum. The sulphurous gas was eliminated by the lungs, causing remarkably beneficial effects. . . .

Dr. Bergeon's method is novel, and with so many strong endorsements it plainly deserves an extended trial. It is not one that can be widely used at present, owing to the care and time needed for its application.

SOME PEDIATRIC PAPERS IN VOLUME 31

Peripheral Neuritis and the Painful Paralyses of Early Life, Henry Dwight Chapin. M.A., M.D.

The Antiseptic Treatment of Summer Diarrhoea, L. Emmett Holt, A.M., M.D.

The Treatment of Empyema in Children, With Particular Reference to the Relative Advantages of Aspiration and Incision, L. Emmett Holt, A.M., M.D.

Acute Empyema in Children, Francis Huber, M.D.

Intubation, Francis Huber, M.D.

Feeding After Intubation of the Larynx, (with exhibition of tubes modified to overcome difficulty in feeding), Joseph O'Dwyer, M.D.

Contribution to the Discussion on Intubation of the Larynx, A. Caillé, M.D.